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DECLARATION

I, Nae MATSUDA, Patent Attorney, of NAKAMURA & PARTNERS, 3-1, Marunouchi 3-chome, Chiyoda-ku, Tokyo, Japan, hereby certify that I am the translator of the basic Japanese Patent Application No. 2001-263718(263718/2001) filed on August 31, 2001 and that the following is a true and correct translation to the best of my knowledge and belief.

Nae Matsuda

Nae MATSUDA
Patent Attorney

Dated: September 4, 2008

JAPAN PATENT OFFICE

This is to certify that the annexed is a true copy of the following application as filed with this office.

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Applicant(s): AJINOMOTO CO., INC.

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Yasuo IMAI

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【Inventor】
【Address】 c/o Central Research Laboratories, Ajinomoto Co., Inc., No.1-1 Suzuki-cho, Kawasaki-ku, Kawasaki-shi, Kanagawa-ken
【Name】 Takashi YAMAMOTO
【Inventor】
【Address】 c/o Central Research Laboratories, Ajinomoto Co., Inc., No.1-1 Suzuki-cho, Kawasaki-ku, Kawasaki-shi, Kanagawa-ken
【Name】 Seiji NIWA
【Inventor】
【Address】 c/o Central Research Laboratories, Ajinomoto Co., Inc., No.1-1 Suzuki-cho, Kawasaki-ku, Kawasaki-shi, Kanagawa-ken
【Name】 Kayo OTANI
【Inventor】
【Address】 c/o Central Research Laboratories, Ajinomoto Co., Inc., No.1-1 Suzuki-cho, Kawasaki-ku, Kawasaki-shi, Kanagawa-ken
【Name】 Seiji OHNO
【Inventor】
【Address】 c/o Central Research Laboratories, Ajinomoto Co., Inc., No.1-1 Suzuki-cho, Kawasaki-ku, Kawasaki-shi, Kanagawa-ken
【Name】 Hajime KOGANEI
【Inventor】
【Address】 c/o Central Research Laboratories, Ajinomoto Co., Inc., No.1-1 Suzuki-cho, Kawasaki-ku, Kawasaki-shi, Kanagawa-ken
【Name】 Satoshi IWAYAMA
【Inventor】
【Address】 c/o Central Research Laboratories, Ajinomoto Co., Inc., No.1-1 Suzuki-cho, Kawasaki-ku, Kawasaki-shi, Kanagawa-ken
【Name】 Akira TAKAHARA
【Inventor】
【Address】 c/o Central Research Laboratories, Ajinomoto Co., Inc., No.1-1 Suzuki-cho, Kawasaki-ku, Kawasaki-shi, Kanagawa-ken
【Name】 Yukitsugu ONO
【Inventor】
【Address】 c/o Central Research Laboratories, Ajinomoto Co., Inc., No.1-1 Suzuki-cho, Kawasaki-ku, Kawasaki-shi, Kanagawa-ken
【Name】 Tomoko TAKEDA
【Inventor】
【Address】 c/o Central Research Laboratories, Ajinomoto Co., Inc., No.1-1 Suzuki-cho, Kawasaki-ku, Kawasaki-shi, Kanagawa-ken
【Name】 Shinichi FUJITA

【Applicant 】
【Discrimination Number 】 000000066
【Name】 Ajinomoto Co., Inc.
【Agent】
【Discrimination Number 】 100059959
【Patent Attorney】
【Name】 Minoru NAKAMURA
【Agent】
【Discrimination Number 】 100067013
【Patent Attorney】
【Name】 Fumiaki OHTSUKA
【Agent】
【Discrimination Number 】 100082005
【Patent Attorney】
【Name】 Yoshio KUMAKURA
【Agent】
【Discrimination Number 】 100065189
【Patent Attorney】
【Name】 Kaichi SHISHIDO
【Agent】
【Discrimination Number 】 100096194
【Patent Attorney】
【Name】 Hideto TAKEUCHI
【Agent】
【Discrimination Number 】 100074228
【Patent Attorney】
【Name】 Toshio IMASHIRO
【Agent】
【Discrimination Number 】 100084009
【Patent Attorney】
【Name】 Nobuo OGAWA
【Agent】
【Discrimination Number 】 100082821
【Patent Attorney】
【Name】 Hiroo MURAKOSO
【Agent】
【Discrimination Number 】 100086771
【Patent Attorney】
【Name】 Takaki NISHIJIMA
【Agent】
【Discrimination Number 】 100084663
【Patent Attorney】
【Name】 Atsushi HAKODA

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【Name of Material】	Specification	1
【Name of Material】	Abstract	1

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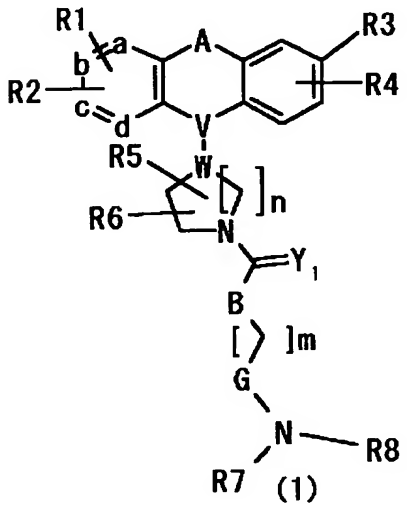
[Name of the Document] SPECIFICATION

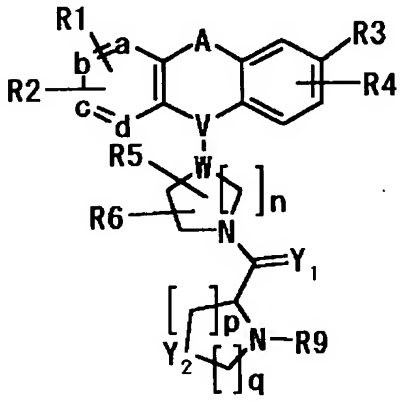
[Title of the Invention] Novel Diarylalkene Derivatives and Novel Diarylalkyl Derivatives

[Claims]

[Clam 1] Diarylalkene derivatives or diarylalkyl derivatives of the following general formula (1), (2), (3) or (4), or pharmaceutically acceptable salts thereof:



(1)



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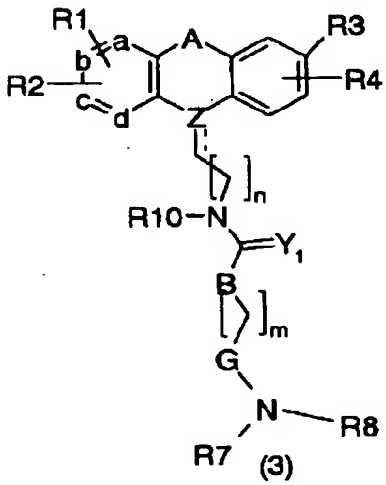

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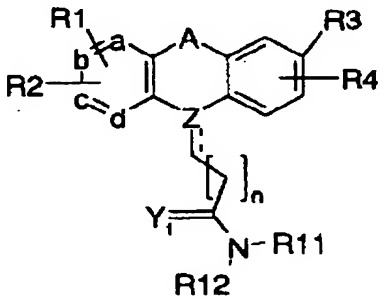


(4)

wherein A represents -CH=CH-, -CH_2-CH_2-, -S-, -CH_2-S-, -S-CH_2-, -O-, -CH_2-O-, -O-CH_2-, -N(R^{17})-CH_2- wherein R^{17} represents H, a lower alkyl or an aryl, -CH_2-N(R^{17})-, -CH=CH-CH_2-, -CH_2-CH=CH-, -CH_2-CH_2-CH_2-,

$-N(R^{17})-(CO)-$, $-(CO)-N(R^{17})-$, $-(CO)-$, $-(SO)-$ or $-C(R^{18}R^{19})-$ wherein R^{18} and R^{19} are each independently selected from the group consisting of H, a lower alkyl, an aryl and $-C(O)OR^{15}$ wherein R^{15} represents a lower alkyl or an aryl;

a, b, c and d are each selected from the group consisting of CR^1 and CR^2; or one of a, b, c and d is N;

R^1 and R^2 each independently represent H, a halogen, $-CF_3$, $-OR^{14}$ wherein R^{14} represents H, a lower alkyl, an aryl or an aryl-lower alkyl group, $-COR^{14}$, $-SR^{14}$, $-S(O)_tR^{15}$ wherein R^{15} represents a lower alkyl or an aryl group and t represents 1 or 2 , $-N(R^{14})_2$, $-NO_2$, $-OC(O)R^{14}$, $-CO_2R^{14}$, $-OCO_2R^{14}$, $-CN$, $-NR^{14}COOR^{15}$, $-SR^{15}C(O)OR^{15}$ or $-SR^{15}N(R^{16})_2$ wherein R^{16} is independently selected from the group consisting of H and $-C(O)OR^{15}$;

R^3 represents H;

R^4 is independently selected from H, a halogen, $-CF_3$, $-OR^{14}$ wherein R^{14} represents H, a lower alkyl, an aryl or an aryl-lower alkyl group, $-COR^{14}$, $-SR^{14}$, $-S(O)_tR^{15}$ wherein t represents 1 or 2 , $-N(R^{14})_2$, $-NO_2$, $-OC(O)R^{14}$, $-CO_2R^{14}$, $-OCO_2R^{14}$, $-CN$, $-NR^{14}COOR^{15}$, $-SR^{15}C(O)OR^{15}$ or $-SR^{15}N(R^{16})_2$ wherein R^{16} is independently selected from the group consisting of H and $-C(O)OR^{15}$;

Z is selected from the group consisting of C, CH and N (with the proviso that when Z is C, the bond represented by a dotted line represents a double bond and when Z is CH or N, the bond represented by the dotted line represents a single bond;

n represents 0 to 3;

R^5 and R^6 each independently represent H, a halogen, $-CF_3$, a lower alkyl or an aryl;

or R^5 and R^6 together form =O or =S;

Y^1 represents O or S;

B represents NR^{17}, CHR^{21}-, CH_2CHR^{21} wherein R^{21} represents H, a lower alkyl, an aryl; a hydroxyl-lower alkyl, -CH_2SH, -$CH_2CH_2SCH_3$, -$CH_2(CO)NH_2$, -$CH_2CH_2(CO)NH_2$, -CH_2COOH, -CH_2CH_2COOH, -$(CH_2)_4NH_2$, -$(CH_2)_3NHC(NH_2)$=NH, benzyl, 4-hydroxybenzyl, 3-indoylmethyl or 5-imidazoylmethyl;

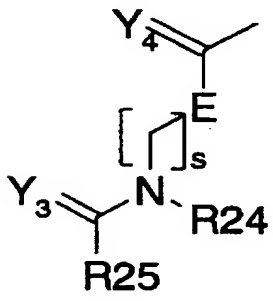
G represents -(CO)-, -(SO)-, -(SO_2)- or a covalent bond;

m represents 0 to 6;

Y^2 represents C or S;

p and q are each independently selected from the group consisting of 1, 2 and 3;

R^7 and R^8 each independently represent H, a lower alkyl, an aryl, -$(CO)R^{18}$ wherein R^{18} represents H, a lower alkyl or an aryl, -$(CS)R^{18}$, -$(CO)NR^{18}R^{19}$, -$(CS)NR^{18}R^{19}$ wherein R^{19} represents H, a lower alkyl or an aryl; or R^{18} and R^{19} together form a cycloalkyl which may have a halogen, -CF_3, a lower alkyl or an aryl as a substituent, -$(CO)OR^{20}$ wherein R^{20} represents an alkyl group having 1 to 12 carbon atoms, an aryl group or a cycloalkyl group which may have a hetero atom in the ring, -$(CS)OR^{20}$ or a group of the following general formula (5):



(5)

wherein Y^4 and Y^3 each represent O or S; s represents 0 to 6;

E represents NR^{22} or CHR^{23} wherein R^{22} represents H, a lower alkyl or

aryl; and R^{23} represents H, a lower alkyl, an aryl, a hydroxyl-lower alkyl, $-CH_2SH$, $-CH_2CH_2SCH_3$, $-CH_2(CO)NH_2$, $-CH_2CH_2(CO)NH_2$, $-CH_2COOH$, $-CH_2CH_2COOH$, $-(CH_2)_4NH_2$, $-(CH_2)_3NHC(NH_2)=NH$, benzyl, 4-hydroxybenzyl, 3-indoylmethyl or 5-imidazoylmethyl;

R^{24} represents H, a lower alkyl or an aryl;

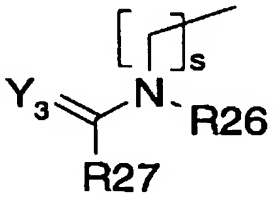
R^{25} represents H, a lower alkyl, an aryl, $-(CO)R^{18}$, $-(CS)R^{18}$, $-(CO)NR^{18}R^{19}$, $-(CS)NR^{18}R^{19}$, $-(CO)OR^{20}$ or $-(CS)OR^{20}$,

R^9 represents H, a lower alkyl, an aryl, $-(CO)R^{18}$, $-(CS)R^{18}$, $-(CO)NR^{18}R^{19}$, $-(CS)NR^{18}R^{19}$, $-(CO)OR^{20}$ or $-(CS)OR^{20}$;

R^{10} represents H, a lower alkyl or an aryl;

R^{11} represents H, a lower alkyl or an aryl;

R^{12} represents H, a lower alkyl, an aryl, $-(CO)R^{18}$, $-(CS)R^{18}$, $-(CO)NR^{18}R^{19}$, $-(CS)NR^{18}R^{19}$, $-(CO)OR^{20}$ or $-(CS)OR^{20}$ or a substituent represented by the following general formula (6):



(6)

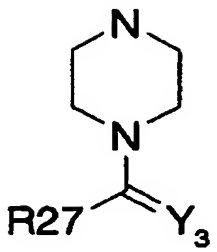
wherein s represents 1 to 6;

Y^3 represents O or S,

R^{26} represents H, a lower alkyl or an aryl;

R^{27} represents H, a lower alkyl, an aryl, $-(CO)R^{18}$, $-(CS)R^{18}$, $-(CO)NR^{18}R^{19}$, $-(CS)NR^{18}R^{19}$, $-(CO)OR^{20}$ or $-(CS)OR^{20}$;

or R^{11} and R^{12} form a substituent represented by the following general formula (7) together with the nitrogen atom:



(7)

[Clam 2] Diarylalkene derivatives or diarylalkyl derivatives, or pharmaceutically acceptable salts according to claim 1, wherein in the above general formulae (1), (2), (3) and (4),

A represents -CH=CH-, -CH_2-CH_2-, -S-, -CH_2-S- or -S-CH_2-;

a, b, c and d each represent CH;

R^3 and R^4 each representH;

Z is selected from the group consisting of C, CH and N (with the proviso that when Z is C, the bond represented by a dotted line represents a double bond and when Z is CH or N, the bond represented by the dotted line represents a single bond);

R^5 and R^6 each representH;

or R^5 and R^6 together form =O;

n represents 1 or 2;

Y^1 represents O;

B represents NR^{17}, CHR^{21}- or, CH_2CHR^{21} wherein R^{21} represents H, a lower alkyl, an aryl or -CH_2OH;

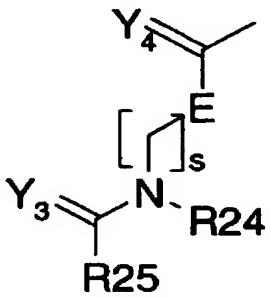
G represents -(CO)- or a covalent bond;

m represents 0 to 6;

p and q are each 1;

R^7 and R^8 each independently represent H, a lower alkyl, an aryl, -(CO)R^{18} wherein R^{18} represents H, a lower alkyl or an aryl,

-(CO)NR^{18}R^{19} wherein R^{19} represents H, a lower alkyl or an aryl; or R^{18} and R^{19} together form a cycloalkyl which may have a halogen, -CF$_3$, a lower alkyl or an aryl as a substituent, -(CO)OR^{20} wherein R^{20} represents an alkyl group having 1 to 12 carbon atoms, an aryl group or a cycloalkyl group which may contain a hetero atom in the ring, or a group of the following general formula (8):



(8)

[wherein Y^4 and Y^3 each represent O;

s represents 1 or 2;

E represents CHR^{23} wherein R^{23} represents H,

R^{24} represents H;

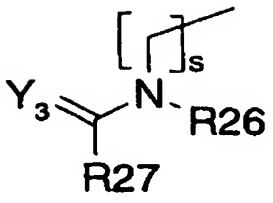
R^{25} represents -(CO)OR^{20};]

R^9 represents -(CO)OR^{20};

R^{10} represents H;

R^{11} represents H;

R^{12} represents a substituent represented by the following general formula (9);



(9)

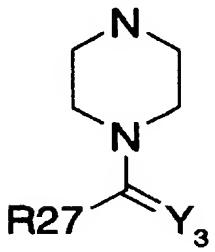
wherein s represents 2 or 3;

Y3 represents O;

R^{26} represents H;

and R^{27} represents -(CO)OR^{20},

or R^{11} and R^{12} form a substituent represented by the following general formula (10) together with the nitrogen atom.



(10)

[Clam 3] Diarylalkene derivatives or diarylalkyl derivatives, or pharmaceutically acceptable salts thereof according to claim 2, wherein in the above general formula (1),

A represents -CH=CH- or -CH_2-CH_2-,

a, b, c and d each represent CH;

R^1 and R^2 each represent H;

R^3 and R^4 each represent H;

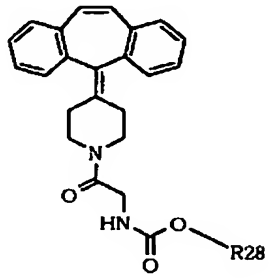
Z is C, the bond represented by a dotted line represents a double bond;

n represents 2;

R^5 and R^6 each represent H; and

Y^1 represents O.

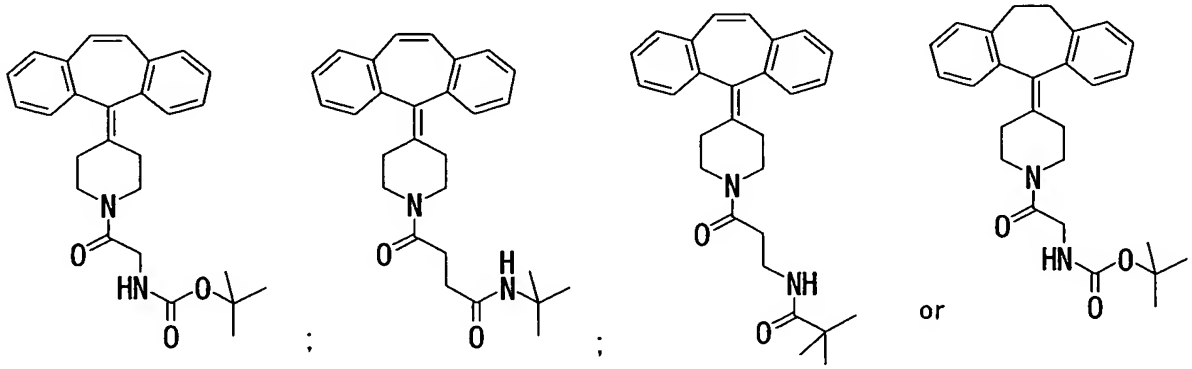
[Clam 4] Diarylalkene derivatives or diarylalkyl derivatives represented by the following general formula (11), or pharmaceutically acceptable salts thereof:



(11)

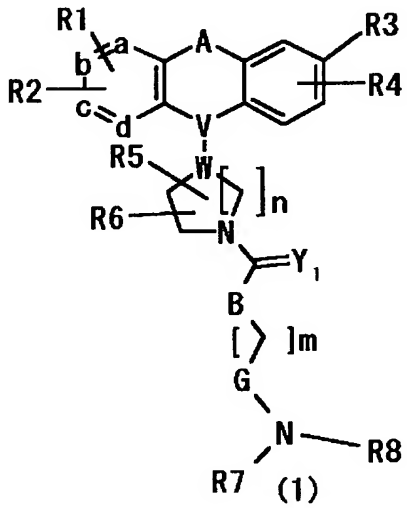
wherein R^{28} represents an alkyl group having 1 to 12 carbon atoms, a cycloalkyl group having 1 to 12 carbon atoms or a cycloalkyl group which may have a hetero atom in the ring.

[Clam 5] Diarylalkene derivatives or diarylalkyl derivatives of the following general formulae, or pharmaceutically acceptable salts thereof:

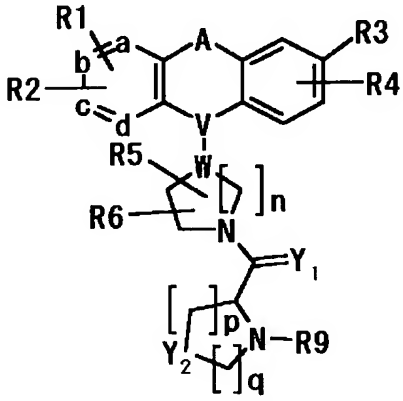


[Clam 6] A therapeutic agent for diseases selected from brain injury caused by ischemia at the acute stage after the onset of cerebral

infarction or cerebral hemorrhage, Alzheimer's disease, AIDS related dementia, Parkinson's disease, progressive neurodegenerative diseases, neuropathy caused by head injury, pain caused by spinal injury or diabetes, neuropathic pain, migraine, visceral pain, cancerous pain, bronchial asthma, unstable angina, irritable colitis or withdrawal symptoms after addiction to drugs, which comprises a diarylalkene derivative or a diarylalkyl derivative of the following general formula (1), (2), (3) or (4), or a pharmaceutically acceptable salt thereof as the active ingredient:



(1)



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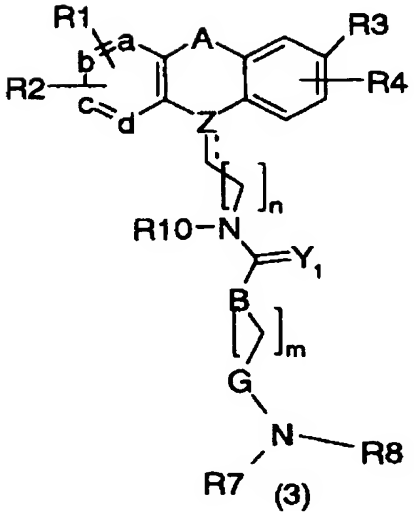

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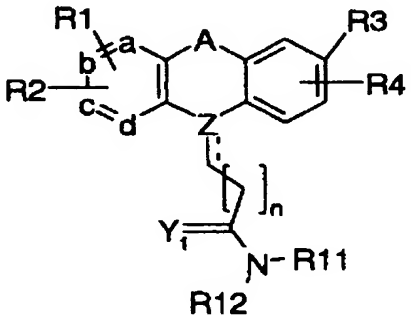


(4)

wherein A represents -CH=CH-, -CH_2-CH_2-, -S-, -CH_2-S-, -S-CH_2-, -O-, -CH_2-O-, -O-CH_2-, -N(R^{17})-CH_2- wherein R^{17} represents H, a lower alkyl or an aryl, -CH_2-N(R^{17})-, -CH=CH-CH_2-, -CH_2-CH=CH-, - CH_2-CH_2-CH_2-, -N(R^{17})-(CO)-, -(CO)-N(R^{17})-, -(CO)-, -(SO)-, -C($R^{18}R^{19}$)- wherein R^{18} and R^{19} are each independently selected from the group consisting of H, a lower alkyl, an aryl and -C(O)OR^{15} wherein R^{15} represents a lower alkyl or an aryl;

a, b, c and d are each independently selected from the group consisting of CR^1 and CR^2;

or one of a, b, c and d is N;

R^1 and R^2 each independently represent H, a halogen, -CF_3, -OR^{14} wherein R^{14} represents H, a lower alkyl, an aryl or an aryl-lower alkyl group, -C(O)R^{14}, -SR^{14}, -$S(O)_t$ R^{15} wherein t represents 1 or 2, -N(R^{14})$_2$, -NO_2, -OC(O)R^{14}, -CO_2R^{14}, -OCO_2R^{14}, -CN, -NR^{14}COOR^{15}, -SR^{15}C(O)OR^{15} or -SR^{15}N(R^{16})$_2$ wherein R^{16} is independently selected from the group consisting of H and -C(O)OR^{15};

R^3 and R^4 each independently represent H, a halogen, -CF_3, -OR^{14} wherein R^{14} represents H, a lower alkyl, an aryl or an aryl-lower alkyl group, -C(O)R^{14}, -SR^{14}, -$S(O)_t$$R^{15}$ wherein t represents 1 or 2, -N(R^{14})$_2$, -NO_2, -OC(O)R^{14}, -CO_2R^{14}, -OCO_2R^{14}, -CN, -NR^{14}COOR^{15}, -SR^{15}C(O)OR^{15} or -SR^{15}N(R^{16})$_2$ wherein R^{16} is independently selected from the group consisting of H and -C(O)OR^{15};

Z is selected from the group consisting of C, CH and N (with the proviso that when Z is C, the bond represented by a dotted line represents a double bond and when Z is CH or N, the bond represented by the dotted line represents a single bond;

n represents 0 to 3;

R^5 and R^6 each represent H, a halogen, -CF_3, a lower alkyl or an aryl;

or R^5 and R^6 together represent =O or =S;

Y^1 represents O or S;

B represents NR^{17}, CHR^{21}, CH_2CHR^{21} wherein R^{21} represents H, a lower alkyl, an aryl, a hydroxyl-lower alkyl, $-CH_2SH$, $-CH_2CH_2SCH_3$, $-CH_2(CO)NH_2$, $-CH_2CH_2(CO)NH_2$, $-CH_2COOH$, $-CH_2CH_2COOH$, $-(CH_2)_4NH_2$, $-(CH_2)_3NHC(NH_2)=NH$, benzyl, 4-hydroxybenzyl, 3-indoylmethyl or 5-imidazoylmethyl;

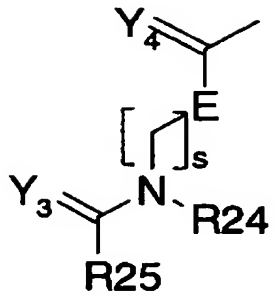
G represents $-(CO)-$, $-(SO)-$, $-(SO_2)-$ or a covalent bond;

m represents 0 to 6;

Y^2 represents C or S;

p and q are each independently selected from the group consisting of 1, 2 and 3;

R^7 and R^8 each independently represent H, a lower alkyl, an aryl, $-(CO)R^{18}$ wherein R^{18a} represents H, a lower alkyl or an aryl, $-(CS)R^{18}$, $-(CO)NR^{18}R^{19}$, $-(CS)NR^{18}R^{19}$ wherein R^{19} represents H, a lower alkyl or an aryl; or R^{18} and R^{19} together form a cycloalkyl which may have a halogen, $-CF_3$, a lower alkyl or an aryl as a substituent, $-(CO)OR^{20}$ wherein R^{20} represents an alkyl group having 1 to 12 carbon atoms, an aryl, a cycloalkyl group which may have a hetero atom in the ring, an aryl-lower alkyl group, $-(CS)OR^{20}$ or a group of the following general formula (5):



(5)

wherein Y^4 and Y^3 each represent O or S; s represents 0 to 6;

E represents NR^{22} or CHR^{23} wherein R^{22} represents H, a lower alkyl or an aryl; and R^{23} represents H, a lower alkyl, an aryl, a hydroxyl-lower alkyl, $-CH_2SH$, $-CH_2CH_2SCH_3$, $-CH_2(CO)NH_2$, $-CH_2CH_2(CO)NH_2$, $-CH_2COOH$, $-CH_2CH_2COOH$, $-(CH_2)_4NH_2$, $-(CH_2)_3NHC(NH_2)=NH$, benzyl, 4-hydroxybenzyl, 3-indoylmethyl or 5-imidazoylmethyl;

R^{24} represents H, a lower alkyl or an aryl;

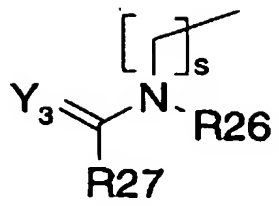
R^{25} represents H, a lower alkyl, an aryl, $-(CO)R^{18}$, $-(CS)R^{18}$, $-(CO)NR^{18}R^{19}$, $-(CS)NR^{18}R^{19}$, $-(CO)OR^{20}$ or $-(CS)OR^{20}$;

R^9 represents H, a lower alkyl, an aryl, $-(CO)R^{18}$, $-(CS)R^{18}$, $-(CO)NR^{18}R^{19}$, $-(CS)NR^{18}R^{19}$, $-(CO)OR^{20}$ or $-(CS)OR^{20}$;

R^{10} represents H, a lower alkyl or an aryl;

R^{11} represents H, a lower alkyl or an aryl;

R^{12} represents H, a lower alkyl, an aryl, $-(CO)R^{18}$, $-(CS)R^{18}$, $-(CO)NR^{18}R^{19}$, $-(CS)NR^{18}R^{19}$, $-(CO)OR^{20}$,$-(CS)OR^{20}$ or a substituent represented by the following general formula (6):



(6)

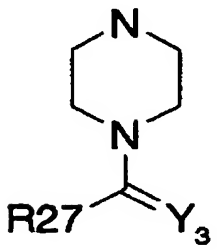
wherein s represents 1 to 6;

Y^3 represents O or S,

R^{26} represents H, a lower alkyl or an aryl;

R^{27} represents H, a lower alkyl, an aryl, -(CO)R^{18}, -(CS)R^{18}, -(CO)$NR^{18}R^{19}$, -(CS)$NR^{18}R^{19}$, -(CO)OR^{20} or -(CS)OR^{20};

or R^{11} and R^{12} form a substituent represented by the following general formula (7) together with the nitrogen atom:



(7)

[Clam 7] A therapeutic agent for diseases selected from brain injury caused by ischemia at the acute stage after the onset of cerebral infarction or cerebral hemorrhage, Alzheimer's disease, AIDS related dementia, Parkinson's disease, progressive neurodegenerative diseases, neuropathy caused by head injury, pain caused by spinal injury or diabetes, neuropathic pain, migraine, visceral pain, cancerous pain, bronchial asthma, unstable angina, irritable colitis or withdrawal symptoms after addiction to drugs, which comprises the diarylalkene

derivative or diarylalkyl derivative, or pharmaceutically acceptable salt thereof according to claims selected from 1 to 5 as the active ingredient.

[Clam 8] N-type calcium channels antagonists, which comprises the diarylalkene derivatives or diarylalkyl derivatives, or pharmaceutically acceptable salts thereof according to claim 6.

[Clam 9] N-type calcium channels antagonists, which comprises the diarylalkene derivatives or diarylalkyl derivatives, or pharmaceutically acceptable salts thereof according to claims selected from 1 to 5.

[Clam 10] A pharmaceutical composition comprising one of the diarylalkene derivatives, diarylalkyl derivatives and pharmaceutically acceptable salts thereof according to claims selected from 1 to 5 as the active ingredient.

[Detailed Description of the Invention]

[Technical Field of the Invention]

The present invention relates to novel diarylalkene derivatives and the use of the diarylalkene derivatives as medicines. The present invention also relates to novel diarylalkyl derivatives and the use of the diarylalkyl derivatives as medicines. It was suggested that the activation of N-type calcium channel is concerned with various diseases, for example, brain injury caused by ischemia at the acute stage after the onset of cerebral infarction or cerebral hemorrhage (including subarachnoidal hemorrhage) or the like; progressive neurodegenerative diseases such as Alzheimer's disease, AIDS related dementia Parkinson's disease, dementia due to cerebrovascular disorder and ALS; neuropathy caused by head injury; various pains such as pain caused by spinal injury, diabetes or thromboangitis obliterans, neuropathic pain, migraine, visceral pain, cancerous pain; various diseases associated with

psychogenic stress such as bronchial asthma, unstable angina and irritable colitis; emotional disorder and withdrawal symptoms after addiction to drugs such as ethanol addiction withdrawal symptoms. The compounds of the present invention produces an inhibitory effect on the activation of N-type calcium channel and, therefore the present invention relates to the use of the compounds as therapeutic agents for these diseases.

[Prior Art]

Calcium channels are now classified into subtypes of L, N, P, Q, R and T. Each subtype of calcium channels is organ-specifically distributed. It is known that particularly N-type calcium channel is widely distributed in central nerves, peripheral nerves and adrenomedullary cells and participates in neuronal cell death, regulation of blood catecholamine level and control of senses such as perception.

It was confirmed that peptides, omega conotoxin GVIA and omega conotoxin MVIIA, which are selectively inhibiting N-type calcium channel, inhibit the release of excitatory neurotransmitters in the sliced brain preparation. It was also confirmed in animal experiments that they inhibit the progress of neuronal cell death associated with cerebrovascular disorders. It is generally considered that compounds having inhibitory effect on the N-type calcium channel are clinically effective in the treatment of brain injury caused by ischemia at the acute stage after the onset of cerebral infarction or cerebral hemorrhage (including subarachnoidal hemorrhage); progressive neurodegenerative diseases such as Alzheimer's disease, AIDS related dementia, Parkinson's disease, dementia due to cerebrovascular disorder and ALS; and neuropathy caused by head injury. In addition, it was confirmed in

animal tests that omega conotoxin MVIIA relieves a pain induced by formalin, hot plate and peripheral neuropathy (J. Pharmacol. Exp. Ther. 269, 1117-1123, 1994; J. Pharmacol. Exp. Ther. 274, 666-672, 1995). Accordingly, omega conotoxin MVIIA is considered to be clinically effective against various pains such as pain caused by spinal injury, diabetes or thromboangitis obliterans, neuropathic pain (e.g. post-herpetic neuralgia, diabetic neuropathy, complex regional pain syndrome, branchial plexus avulsion, trigeminal neuralgia, pain caused by spinal injury, restrictive neuropathy, central pain, postoperative pain), migraine, visceral pain, cancerous pain. In addition, because omega conotoxin GVIA inhibits the release of catecholamine from cultured sympathetic ganglion cells, the contraction of the isolated blood vessel by electric stimulation of the perivascular nerve and catecholamine secretion from canine adrenal medulla, it is considered that compounds having inhibitory effect on N-type calcium channel are clinically effective against various diseases related to psychogenic stress such as bronchial asthma, unstable angina and irritable colitis [Neuropharmacol., 32, 1141 (1993)].

Some peptidergic and non-peptidergic compounds which selectively affect N-type calcium channels have been ever disclosed (see, for example, WO 9313128, WO 9849144, WO 9901438 and WO 9932446). However, none of them was actually used as a medicine. Some of the compounds which affect N-type calcium channels are also effective against various types of calcium channels of other than N-type (Br. J. Pharmacol., 122(1), 37-42, 1997). For example, compounds having an antagonistic effect on L-type calcium channels, which are very closely related to hypotensive effect, could not be used for diseases for which N-type antagonists will be used (such as cerebral stroke, neuralgia,

terminal cancer pain and pain caused by spinal injury). Under these circumstances, the development of a highly active antagonist selective toward N-type calcium channels has been eagerly demanded. In addition, an improvement in QOL (quality of life) of patients is demanded and the development of oral medicines is considered to be necessary. In particular, considering the application of the antagonists as analgesics to terminal cancer patients or spinal injury patients, QOL can be expected to be much improved provided that the number of times for the patients to take medicines and dose thereof for patients could be reduced.

However, well-known N-type calcium channel antagonists are yet insufficient for solving this problem, since some of them are peptides that cannot be absorbed from the gastrointestinal tracts or some are decomposed in the gastrointestinal tracts because of their chemical instability.

On the other hand, various diarylalkene derivatives and diarylalkyl derivatives have been reported (WO 8803138, WO 9510516, WO 9630363, WO 95631478, US 5994364 and Japanese Patent Kokai No. Hei 8-291142/1996). However, no literature disclosed that the compounds reported hereinbefore and also diarylalkene derivatives and diarylalkyl derivatives analogous to them have a selective inhibitory effect on N-type calcium channel.

Piperidine derivatives having structures similar to those of the compounds of the present invention are reported in Japanese Patent Kokai No. Hei 8-3135/1996. However, it is also described therein that they are antithrombocytic agents which powerfully inhibit serotonin receptor 2, that because of the antagonistic effect on serotonin, they are effective in the treatment of ischemic diseases, migraine, etc. and that

because of the antithrombocytic effect, they are effective in the treatment of a pain caused by various ischemic diseases and chronic arterial occlusive disease. However, they are essentially different, in the mechanism of the effects, from the N-type calcium channel antagonists directly effective on the neurons to exert the effects on the above-described diseases.

Further, piperidine derivatives having structures similar to those of the compounds of the present invention and effective in the treatment of diseases such as asthma, allergic rhinitis, allergic dermatitis and hives are reported in Japanese Patent Kokai No. Hei 8-291142/1996. However, they are antihistaminic agents or antileukotrienes and essentially different, in the mechanism of the effects, from the N-type calcium channel antagonists directly effective on the neurons to exert the effects on the above-described diseases.

[Problems to be solved by the Invention]

The object of the present invention is to provide new compounds having a selective antagonistic effect on N-type calcium channels.

Another object of the present invention is to provide antagonists to N-type calcium channels.

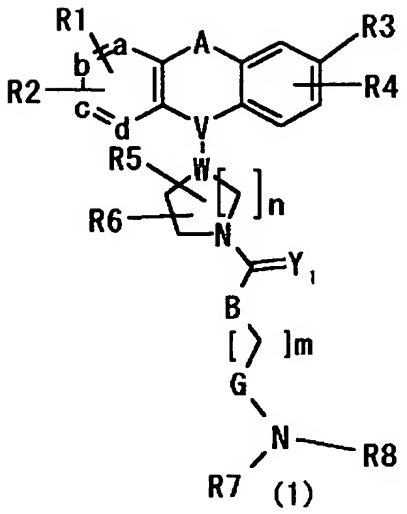
Still another object of the present invention is to provide a method for treating any diseases of brain injury caused by ischemia at the acute stage after the onset of cerebral infarction or cerebral hemorrhage, Alzheimer's disease, AIDS related dementia, Parkinson's disease, progressive neurodegenerative diseases, neuropathy caused by head injury, pain caused by spinal injury or diabetes, neuropathic pain, migraine, visceral pain, cancerous pain, bronchial asthma, unstable angina, irritable colitis and withdrawal symptoms after addiction to

drugs.

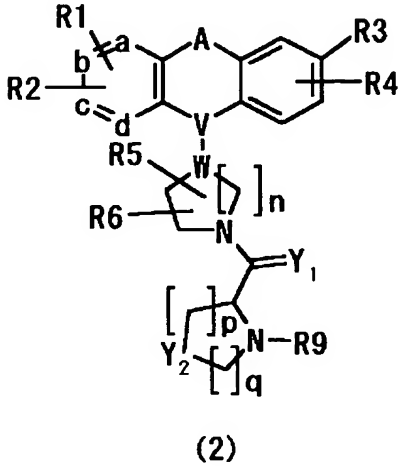
[Means to Solve the Problem]

After synthesizing various novel diarylalkene derivatives and diarylalkyl derivatives and examining the N-type calcium channel inhibitory effect (determined by fluorescent dye method) and L-type calcium channel inhibitory effect (relaxation response against the KCl-induced contraction of isolated rat thoracic aorta) for the purpose of solving the above-described problems, the inventors have found that specified diarylalkene derivatives and diarylalkyl derivatives have an excellent effect of selectively antagonizing N-type calcium channels. The present invention has been completed on the basis of this finding. The compounds of the present invention are orally absorbed and have lasting efficacy and thus, they are usable as therapeutic agents for the above-described diseases.

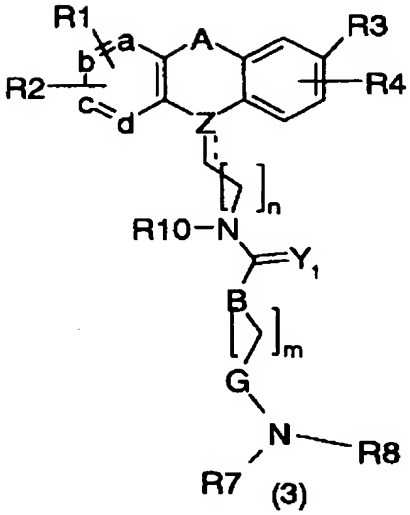
Namely, the present invention provides diarylalkene derivatives or diarylalkyl derivatives of the following general formula (1), (2), (3) or (4), or pharmaceutically acceptable salts thereof, and N-type calcium channel antagonists and a pharmaceutical composition comprising one of them as an active ingredient:



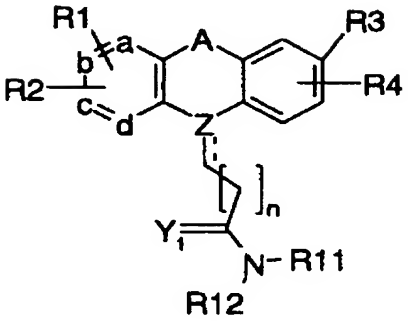
(1)



(2)



(3)



(4)

wherein A represents -CH=CH-, -CH_2-CH_2-, -S-, -CH_2-S-, -S-CH_2-, -O-, -CH_2-O-, -O-CH_2-, -N(R^{17})-CH_2- wherein R^{17} represents H, a lower alkyl or an aryl, -CH_2-N(R^{17})-, -CH=CH-CH_2-, -CH_2-CH=CH-, -CH_2-CH_2-CH_2-, -N(R^{17})-(CO)-, -(CO)-N(R^{17})-, -(CO)-, -(SO)- or -C($R^{18}R^{19}$)- wherein R^{18} and R^{19} are each independently selected from the group consisting of H, a lower alkyl, an aryl and -C(O)OR^{15} wherein R^{15} represents a lower alkyl or an aryl;

a, b, c and d are each independently selected from the group consisting of

CR^1 and CR^2;

or one of a, b, c and d is N;

$R^1$and R^2 each independently represent H, a halogen, $-CF_3$, $-OR^{14}$ wherein R^{14} represents H, a lower alkyl, an aryl or an aryl-lower alkyl group, $-COR^{14}$, $-SR^{14}$-$S(O)_t$ R^{15} wherein R^{15} represents a lower alkyl or an aryl group and t represents 1 or 2, $-N(R^{14})_2$, $-NO_2$, $-OC(O)R^{14}$, $-CO_2R^{14}$, $-OCO_2R^{14}$, -CN, $-NR^{14}COOR^{15}$, $-SR^{15}C(O)OR^{15}$ or $-SR^{15}N(R^{16})_2$ wherein R^{16} is independently selected from the group consisting of H and $-C(O)OR^{15}$;

R^3 represents H;

R^4 represents H, a halogen, $-CF_3$, $-OR^{14}$ wherein R^{14} represents H, a lower alkyl, an aryl or an aryl-lower alkyl group, $-COR^{14}$, $-SR^{14}$, $-S(O)_t$ R^{15} wherein t represents 1 or 2, $-N(R^{14})_2$, $-NO_2$, $-OC(O)R^{14}$, $-CO_2R^{14}$, $-OCO_2R^{14}$, -CN, $-NR^{14}COOR^{15}$, $-SR^{15}C(O)OR^{15}$ or $-SR^{15}N(R^{16})_2$ wherein R^{16} is independently selected from the group consisting of H and $-C(O)OR^{15}$;

Z is selected from the group consisting of C, CH and N (with the proviso that when Z is C, the bond represented by a dotted line represents a double bond and when Z is CH or N, the bond represented by the dotted line represents a single bond;

n represents 0 to 3;

R^5 and R^6 each independently represent H, a halogen, $-CF_3$, a lower alkyl or an aryl;

or R^5 and R^6 together form =O or =S;

Y^1 represents O or S;

B represents NR^{17}, CHR^{21}, CH_2CHR^{21} wherein R^{21} represents H, a lower alkyl, an aryl, a hydroxyl-lower alkyl, $-CH_2SH$, $-CH_2CH_2SCH_3$, $-CH_2(CO)NH_2$, $-CH_2CH_2(CO)NH_2$, $-CH_2COOH$, $-CH_2CH_2COOH$,

$-(CH)_4NH_2$, $-(CH_2)_3NHC(NH_2)=NH$, benzyl, 4-hydroxybenzyl, 3-indoylmethyl or 5-imidazoylmethyl;

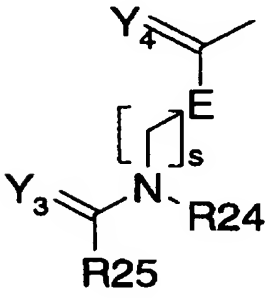
G represents $-(CO)-$, $-(SO)-$, $-(SO_2)-$ or a covalent bond;

m represents 0 to 6;

Y^2 represents C or S;

p and q are each independently selected from the group consisting of 1, 2 and 3;

R^7 and R^8 each represent H, a lower alkyl, an aryl, $-(CO)R^{18}$ wherein R^{18} represents H, a lower alkyl or an aryl, $-(CS)R^{18}$, $-(CO)NR^{18}R^{19}$, $-(CS)NR^{18}R^{19}$ wherein R^{19} represents H, a lower alkyl or an aryl; or R^{18} and R^{19} together form a cycloalkyl which may have a halogen, $-CF_3$, a lower alkyl or an aryl as a substituent, $-(CO)OR^{20}$ wherein R^{20} represents an alkyl group having 1 to 12 carbon atoms, an aryl group or a cycloalkyl group which may have a hetero atom in the ring, $-(CS)OR^{20}$ or a group of the following general formula (5):



(5)

wherein Y^4 and Y^3 each represent O or S; s represents 0 to 6;

E represents NR^{22} or CHR^{23} wherein R^{22} represents H, a lower alkyl or aryl; and R^{23} represents H, a lower alkyl, an aryl, a hydroxyl-lower alkyl, $-CH_2SH$, $-CH_2CH_2SCH_3$, $-CH_2(CO)NH_2$, $-CH_2CH_2(CO)NH_2$, $-CH_2COOH$, $-CH_2CH_2COOH$, $-(CH_2)_4NH_2$, $-(CH_2)_3NHC(NH_2)=NH$, benzyl,

4-hydroxybenzyl, 3-indoylmethyl or 5-imidazoylmethyl;

R^{24} represents H, a lower alkyl or an aryl;

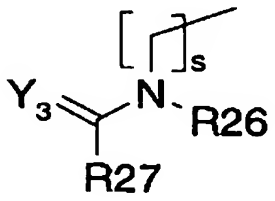
R^{25} represents H, a lower alkyl, an aryl, -(CO)R^{18}, -(CS)R^{18}, -(CO)$NR^{18}R^{19}$, -(CS)$NR^{18}R^{19}$, -(CO)OR^{20} or -(CS)OR^{20};

R^{9} represents H, a lower alkyl, an aryl, -(CO)R^{18}, -(CS)R^{18}, -(CO)$NR^{18}R^{19}$, -(CS)$NR^{18}R^{19}$, -(CO)OR^{20} or -(CS)OR^{20};

R^{10} represents H, a lower alkyl or an aryl;

R^{11} represents H, a lower alkyl or an aryl;

R^{12} represents H, a lower alkyl, an aryl, -(CO)R^{18}, -(CS)R^{18}, -(CO)$NR^{18}R^{19}$, -(CS)$NR^{18}R^{19}$, -(CO)OR^{20},-(CS)OR^{20} or a substituent represented by the following general formula (6):



(6)

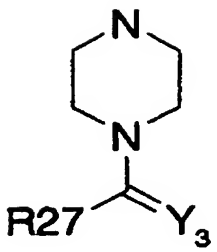
wherein s represents 1 to 6;

Y^{3} represents O or S,

R^{26} represents H, a lower alkyl or an aryl;

R^{27} represents H, a lower alkyl, an aryl, -(CO)R^{18}, -(CS)R^{18}, -(CO)$NR^{18}R^{19}$, -(CS)$NR^{18}R^{19}$, -(CO)OR^{20} or -(CS)OR^{20};

or R^{11} and R^{12} form a substituent represented by the following general formula (7) together with the nitrogen atom.



(7)

The present invention also provides a therapeutic agent for any diseases of brain injury caused by ischemia at the acute stage after the onset of cerebral infarction or cerebral hemorrhage, Alzheimer's disease, AIDS related dementia, Parkinson's disease, progressive neurodegenerative diseases, neuropathy caused by head injury, pain caused by spinal injury or diabetes, neuropathic pain, migraine, visceral pain, cancerous pain, bronchial asthma, unstable angina, irritable colitis and withdrawal symptoms after addiction to drugs, comprising the above-described diarylalkene derivative or diarylalkyl derivative of formula (1), (2), (3) or (4) wherein R^3 represents the same group as that defined in R^4, and R^{20} represents an alkyl group having 1 to 12 carbon atoms, an aryl group, a cycloalkyl group which may have a hetero atom in the ring or an aryl-lower alkyl group, or a pharmaceutically acceptable salt thereof, as the active ingredient.

[Embodiment of the Invention]

The term "lower" herein indicates that the group has 1 to 6 carbon atoms. Alkyl groups themselves and also alkyl groups in alkenyl groups, alkinyl groups, alkoxy groups, alkylamino groups, alkylthio groups, alkanoyl groups may be either linear or branched. Examples of these alkyl groups are methyl group, ethyl group, propyl group, isopropyl

group, butyl group, pentyl group, hexyl group, and secondary and tertiary butyl groups. In them, those having 1 to 4 carbon atoms are preferred. The aryl-lower alkyl groups include, for example, benzyl group. The hetero atoms include nitrogen, oxygen, sulfur, etc. The halogen atoms include fluorine, chlorine, bromine and iodine. In the present specification, the aryl groups are both substituted and unsubstituted aryl groups. They are preferably phenyl or substituted phenyl and, in particular, halogens, alkyl and alkoxy can be considered to be substituents therefor. The cycloalkyl groups include, for example, cyclopentyl groupand cyclohexyl group. The cycloalkyl groups which may have a hetero atom in the chain include tetrahydropyranyl group, piperidyl group, pyrrolidinyl groupand piperazinyl group.

In the above general formulae (1), (2), (3) and (4), groups represented by A are preferably -CH=CH-, $-CH_2-CH_2-$, -S-, $-CH_2-S-$ and $-S-CH_2-$. They are particularly preferably -CH=CH-.

Each of a, b, c and d is independently preferably CH.

Each of R^1 to R^4 is preferably hydrogen atom.

The group represented by Z is preferably selected from the group consisting of C, CH and N (with the proviso that when Z is C, the bond represented by a dotted line represents a double bond and when Z is CH or N, the bond represented by the dotted line represents a single bond). Z is particularly preferably C.

n preferably represents 1 or 2. It is particularly preferably 2.

Preferably, R^5 and R^6 are each hydrogen atom or they together form =O.

Y^1 preferably represents oxygen atom.

R^{17} in NR^{17} represented by B is preferably hydrogen atom, and R^{21} in CHR^{21} and CH_2CHR^{21} is preferably hydrogen atom or

hydroxymethyl group. The group represented by G is preferably -(CO)- or a covalent bond.

m represents 0 to 6, preferably 0 to 3.

Preferably p and q each independently represent 1, and Y^2 represents carbon atom or sulfur atom.

R^7 and R^8 are preferably hydrogen atom, a lower alkyl, an aryl, $-(CO)R^{18}$ wherein R^{18} represents H, a lower alkyl or an aryl, $-(CO)NR^{18}R^{19}$ wherein R^{19} represents H, an alkyl or an aryl; or R^{18} and R^{19} together form a cycloalkyl which may have a halogen, $-CF_3$, an alkyl or an aryl as a substituent, $-(CO)OR^{20}$ wherein R^{20} represents an alkyl or an aryl. A lower alkyl group of R^{18} is preferably, methyl group, ethyl group, isopropyl group or secondary or tertiary butyl group.

Further, R^7 and R^8 are preferably a group represented by the above general formula (5) wherein s represents1 or 2, E is preferably CHR^{23} wherein Y^4 represent O; R^{23} preferably represents H,; R^{24} preferably represents H, and R^{25} preferably represents $-(CO)OR^{20}$;

R^9 preferably represents $-(CO)OR^{20}$;

R10 preferably represents H;

R11 preferably represents H;

R12 preferably represents a substituent represented by the above general formula (6);

R24 preferably represents H;

R25 preferably represents $-(CO)OR^{20}$;

wherein s preferably represents 2 or 3;

Y^3 preferably represents O;

R26 preferably represents H; and

R27 preferably represents $-(CO)OR^{20}$;

or R^{11} and R^{12} preferably represent a substituent represented by the

above general formula (7) together with nitrogen atom.

In the present invention, particularly preferred diarylalkene derivatives, diarylalkyl derivatives and pharmaceutically acceptable salts of them are those wherein:

A represents -CH=CH- or -CH_2-CH_2-;

a, b, c and d each represent CH;

$R^1$and R^2each represent H;

R^3 and R^4 each represent H;

Z represents C, and the bond represented by a dotted line represents a double bond;

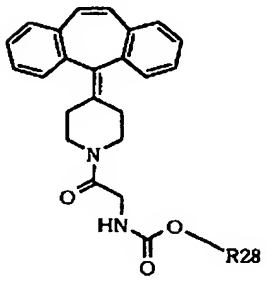
n represents 2;

R^5 and R^6 each represent H; and

Y^1 represents O.

In the compounds of the general formulae (1) to (4) in the present invention, preferred compounds are those of general formula (1) and more preferred compounds are those having the above-described preferred groups.

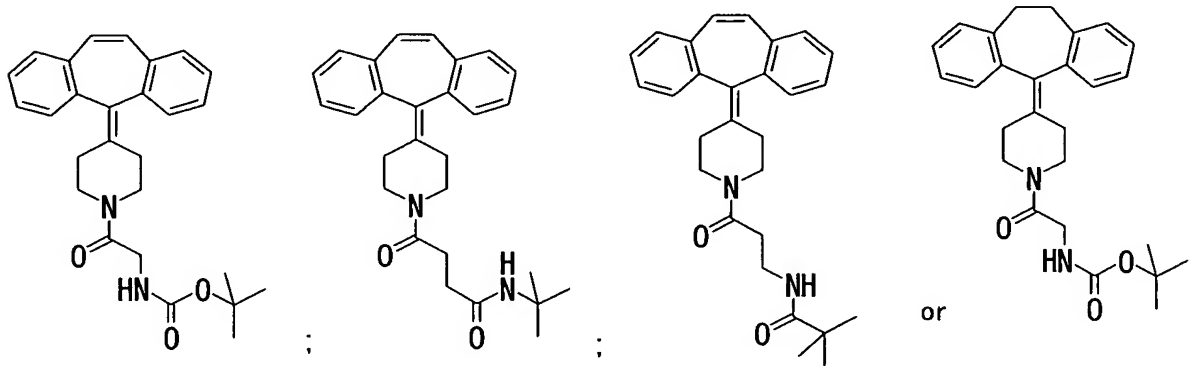
In the compounds of the present invention, diarylalkene derivatives, and diarylalkyl derivatives of the following general formula (11) and pharmaceutically acceptable salts thereof are further preferred:



(11)

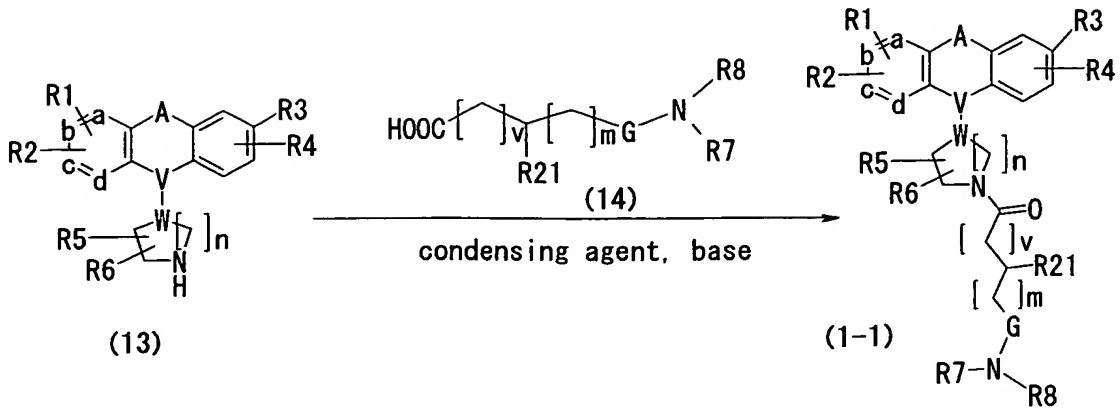
wherein R^{28} represents an alkyl group having 1 to 12 carbon atoms, a cycloalkyl group having 1 to 12 carbon atoms or a cycloalkyl group which may have a hetero atom in the ring. R^{28} is preferably a branched alkyl group, particularly a branched alkyl group having 3 to 8 carbon atoms.

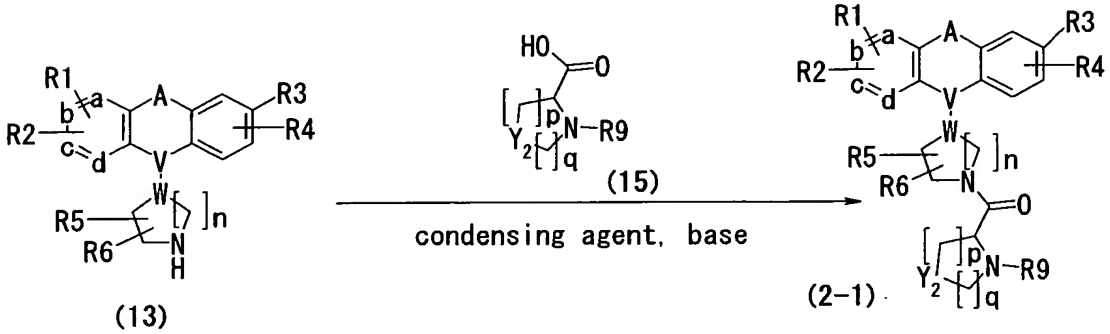
In the present invention, diarylalkene derivatives and diarylalkyl derivatives of the following general formulae and pharmaceutically acceptable salts of them are also preferred:

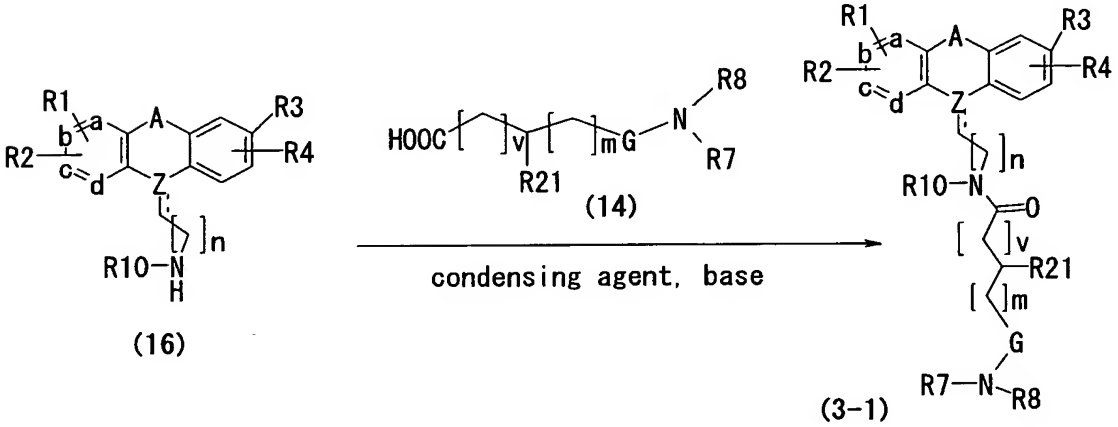


The diarylalkene derivatives and diarylalkyl derivatives (1), (2), (3) and (4) of the present invention can be produced by processes described below.

For example, diarylalkene derivatives and diarylalkyl derivatives (1-1), (2-1) and (3-1) of the general formulae (1), (2) and (3) wherein Y_1 represents oxygen atom, B represents CHR^{21} and R^5 and R^6 do not together form oxygen atom or sulfur atom can be produced as follows:



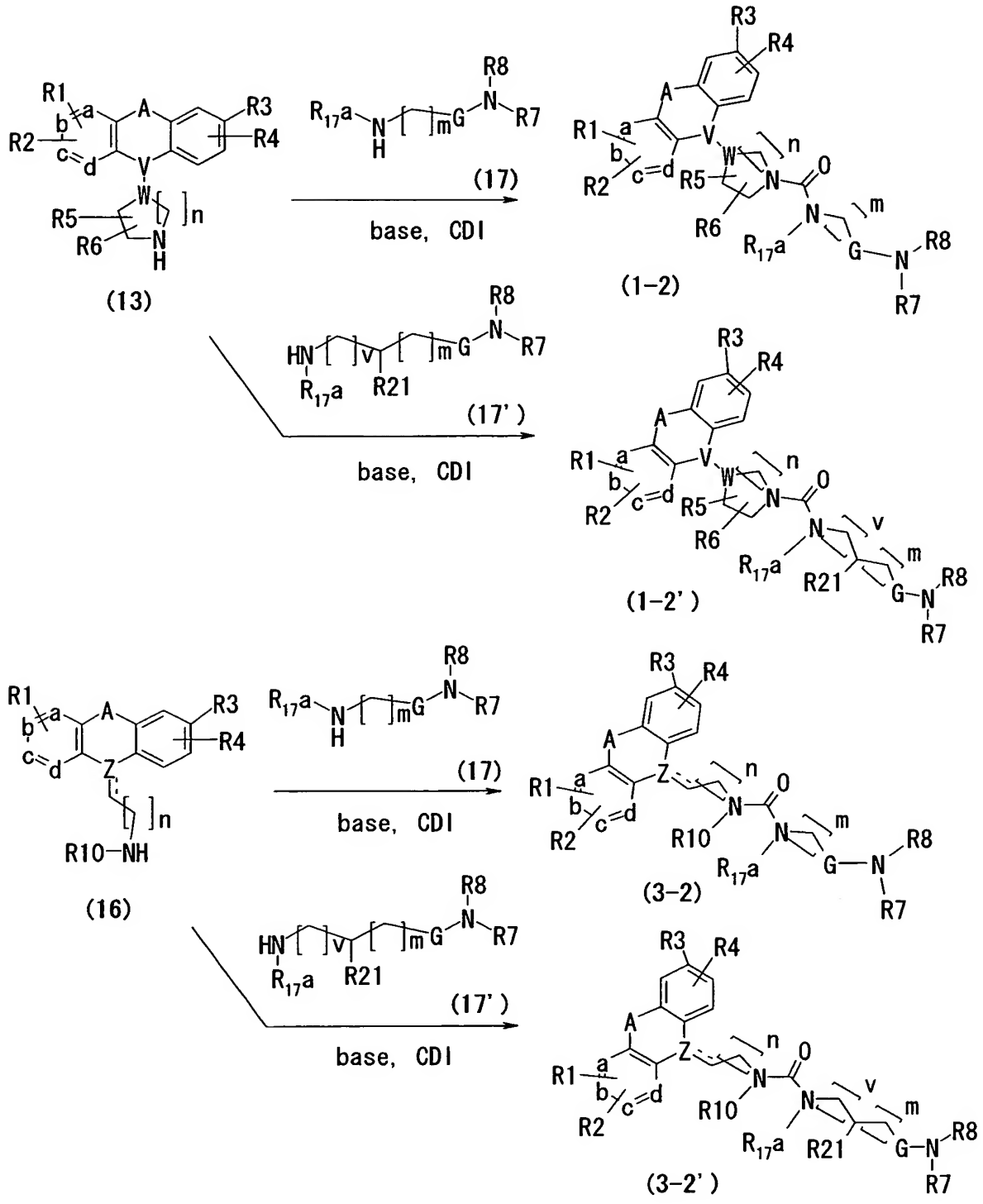




The intended diarylalkene derivatives and diarylalkyl derivatives can be obtained by condensing an amine (13) or (16) with a carboxylic acid (14) or (15) in the presence of a base such as triethylamine and a condensing agent such as 1-ethyl-3-(3'-dimethylaminopropyl) carbodiimide or 1,3-dicyclohexylcarbodiimide.

3-(10,11-Dihydro-5H-dibenzo[a,d][7]-annulen-5-ylidene) pyrrolidinie was synthesized according to [Patent: FR1522934].

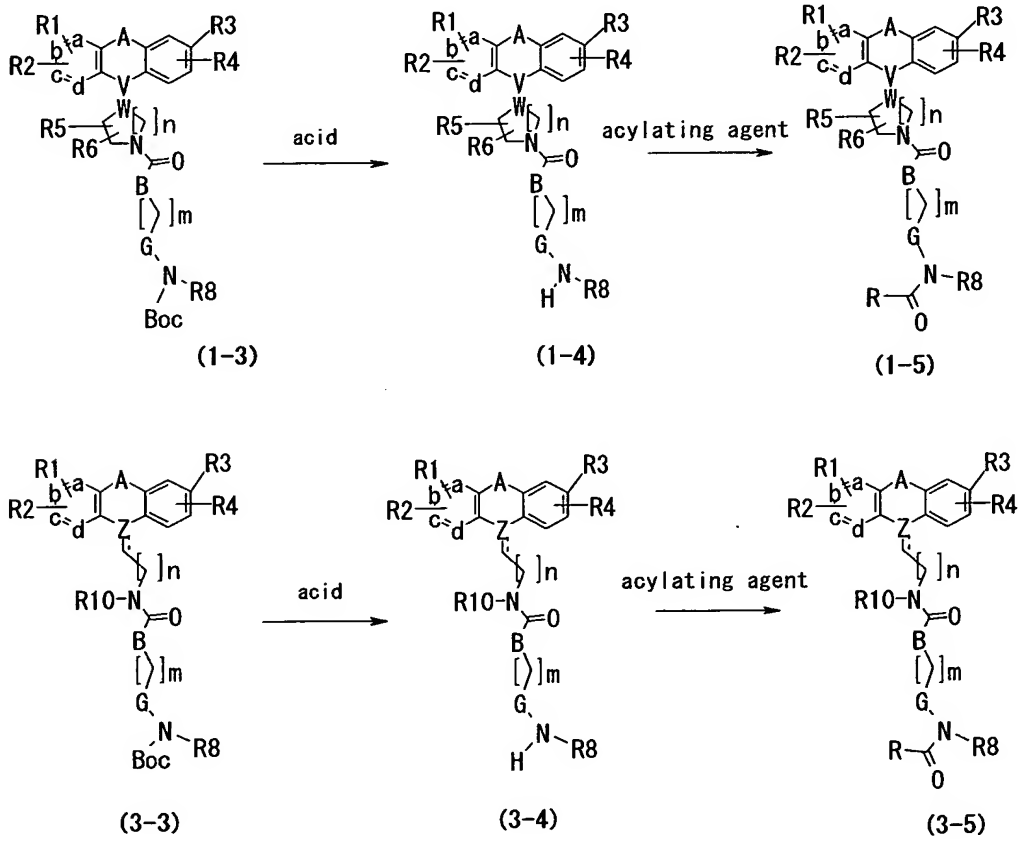
Diarylalkene derivatives and diarylalkyl derivatives (1-2) and (3-2) of the general formulae (1) and (3) wherein Y_1 represents oxygen atom, B represents NR^{17} and R^5 and R^6 do not together form oxygen atom or sulfur atom can be produced as follows:



The intended diarylalkene derivatives and diarylalkyl derivatives can be obtained by reacting an amine (13) or (16) and an amine (17) with

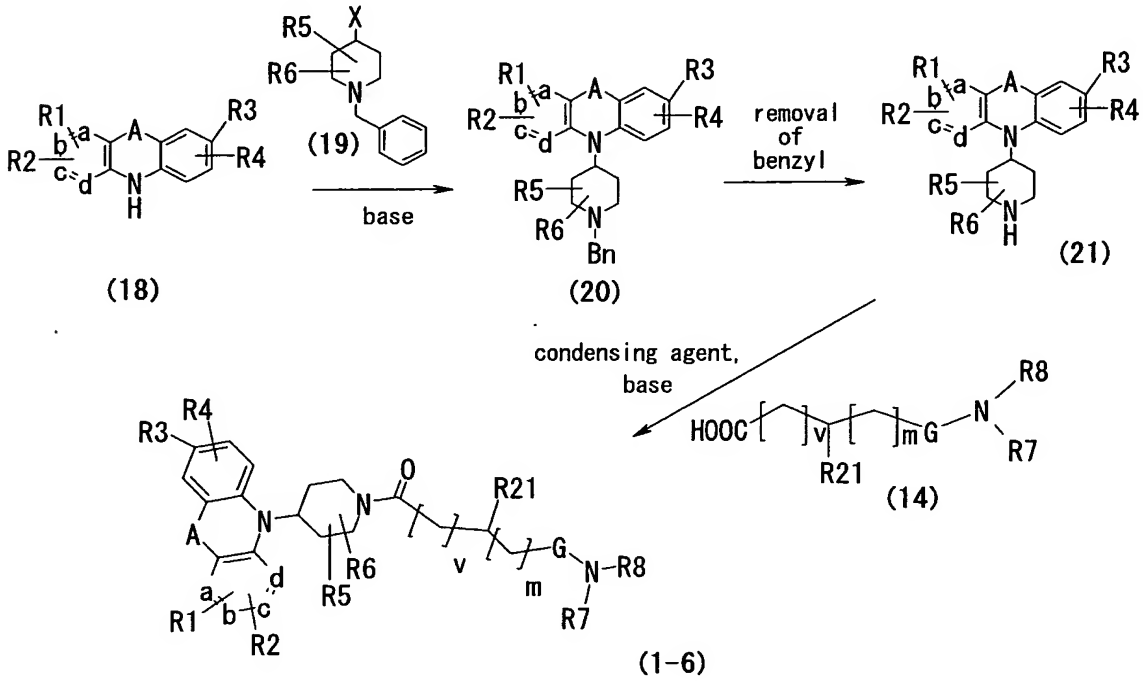
1,1'-carbonylbis-1H-imidazole (CDI) in the presence of a base such as triethylamine.

When compounds (1-3) and (3-3) have t-butoxycarbonyl group (Boc group) as shown below, they can be converted into amines (1-4) and (3-4) by using an acid such as trifluoroacetic acid or hydrochloric acid. Also, they can be acylated with an acylating agent such as an acid chloride, an acid anhydride, a chloroformic ester or carbamoyl chloride in the presence of a base such as triethylamine to obtain diarylalkene derivatives and diarylalkyl derivatives of formulae (1-5) and (3-5):



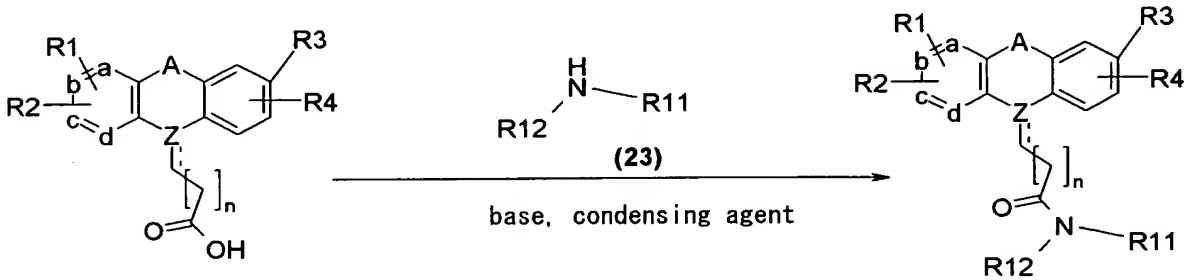
Diarylalkyl derivatives (1-6) of the general formula (1) wherein Y_1 represents oxygen atom, B represents CHR^{21}, Z represents N, n represents 2 and R^5 and R^6 do not together form oxygen atom or sulfur

atom can be produced as shown in the following reaction scheme wherein X represents a halogen such as I, Br or Cl, or a sulfonyloxyl group such as methanesulfonyloxyl group, trifluoromethanesulfonyloxyl group or p-toluenesulfonyloxyl group:



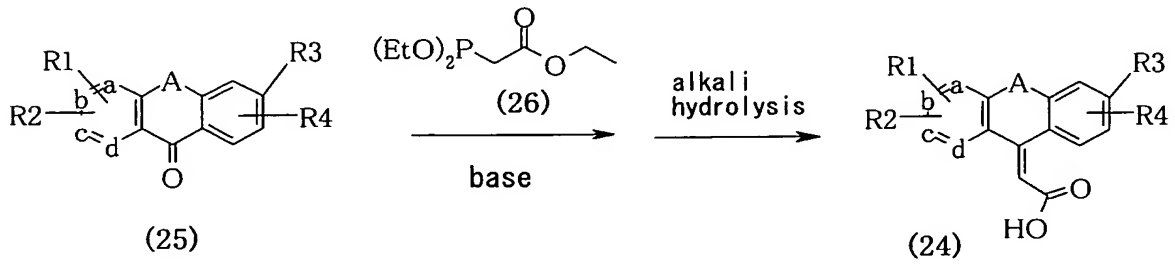
Tertiary aniline derivatives such as those represented by formula (20) can be obtained by reacting an aniline derivative (18) with a sulfonic acid ester or a halide (19) in the presence of a base such as sodium hydride or lithium diisopropylamide. Secondary amines (21) can be obtained by removing benzyl from the compounds (20) in the presence of a catalyst such as palladium carbon, palladium hydroxide carbon or Raney nickel. By condensing the secondary amines (21) with a carboxylic acid (14) in the presence of a base such as triethylamine and a condensing agent such as 1-ethyl-3-(3'-dimethylaminopropyl) carbodiimide or 1,3-dicyclohexylcarbodi-imide, the intended diarylalkene derivatives and diarylalkyl derivatives can be obtained.

When Y_1 in (4) is oxygen atom, the intended diarylalkene derivatives and diarylalkyl derivatives (4-1) can be obtained by, for example, condensing a carboxylic acid (22) with an amine (23) in the presence of a base such as triethylamine and a condensing agent such as 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide or 1,3-dicyclohexyl carbodiimide.



(22) (4-1)

In the compounds (22), those (24) wherein Z is C and n is 0 can be synthesized by, for example, the following reaction scheme:



(25) (24)

The intended compounds (24) can be obtained by, for example, condensing a ketone (25) with ethyl diethylphosphonoacetate (26) in the presence of a base such as sodium hydride or lithium diisopropylamide.

When the compounds of general formulae (1), (2), (3) and (4) of the present invention can form salts thereof, the salts are pharmaceutically acceptable salts such as ammonium salts, salts thereof

with alkali metals, e. g. sodium and potassium, salts thereof with alkaline earth metals, e. g. calcium and magnesium, salts thereof with aluminum or zinc, salts thereof with organic amines, e. g. morpholineand piperidine, salts thereof with basic amino acids, e. g. arginine and lysine.

The compounds of the general formulae (1), (2), (3) and (4) and salts thereof are administered as they are or in the form of various medicinal compositions thereof to the patients. The dosage forms of the medicinal compositions are, for example, tablets, powders, pills, granules, capsules, suppositories, solutions, sugar-coated tablets and depots. They can be prepared with ordinary preparation assistants by an ordinary method. For example, the tablets are prepared by mixing the diarylalkene derivative or diarylalkyl derivative, the active ingredient of the present invention, with any of known adjuvants such as inert diluents, e. g. lactose, calcium carbonate and calcium phosphate; binders, e. g. acacia, corn starch and gelatin; extending agents, e. g. alginic acid, corn starch and pre-gelatinized starch; sweetening agents, e. g. sucrose, lactose and saccharin; corrigents, e. g. peppermint, gaultheria leaves oil and cherry; and lubricants, e. g. magnesium stearate, talc and carboxymethyl cellulose.

The N-type calcium channel antagonist containing one of the compounds of the above general formulae (1), (2), (3) and (4) or one of salts thereof as active ingredient is usable as a therapeutic agent for various diseases, for example, brain injury caused by ischemia at the acute stage after the onset of cerebral infarction or cerebral hemorrhage (including subarachnoidal hemorrhage); progressive neurodegenerative diseases such as Alzheimer's disease, AIDS related dementia, Parkinson's disease, dementia due to cerebrovascular disorder and ALS;

neuropathy caused by head injury; pain caused by spinal injury or diabetes, neuropathic pain, migraine, visceral pain, cancerous pain; various diseases associated with psychogenic stress such as bronchial asthma, unstable angina and irritable colitis; emotional disorder and withdrawal symptoms after addiction to drugs such as ethanol addiction withdrawal symptoms.

The dose of the compounds or salts thereof used for the above-described purpose varies depending on the intended therapeutic effect, administration method, period of the treatment, and age and body weight of the patient. The dose is usually 1 μg to 5 g a day for adults in the oral administration, and 0.01 μg to 1 g a day for adults in the parenteral administration.

Examples

The following Examples will further illustrate the present invention, which by no means limit the invention.

Example 1

Synthesis of t-butyl 2-[4-(5H-dibenzo[a,d][7]annulen-5-ylidene)-1-piperidinyl]-2-oxoethylcarbamate:

3.00 g (10.9 mmol) of 4-(5H-dibenzo[a,d][7]annulen-5-ylidene)-1-piperidine, 2.29 g (13.2 mmol) of N-t-butoxycarbonylglycine, 3.14 g (16.4 mmol) of 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide hydrochloride and 122 mg (1.00 mmol) of 4-dimethylaminopyridine were dissolved in 50 ml of dichloromethane. 2.20 g (3.04 mmol) of triethylamine was added to the obtained solution, and they were stirred overnight. Saturated aqueous sodium hydrogencarbonate solution was added to the obtained mixture. After extracting with dichloromethane 3 times, the organic layer was washed with saturated aqueous sodium

chloride solution. After drying over anhydrous sodium sulfate, the solvent was evaporated under reduced pressure, and the residue was purified by the silica gel chromatography (hexane : ethyl acetate = 4:1 to 2:1) to obtain the title compound.

Yield: 4.29 g (10.2 mmol), 94 %

MS (ESI, m/z) 431 $(M+H)^+$

^{1}H-NMR ($CDCl_3$): 1.44 (9H, s), 2.15-2.35 (4H, m), 3.02 (2H, m), 3.42 (1H, m), 3.81-4.01 (3H, m), 5.51 (1H, br s), 6.92 (2H, s), 7.15-7.38 (8H, m).

Example 2

Synthesis of 2-[4-(5H-dibenzo[a,d][7]annulen-5-ylidene)-1-piperidinyl]-2-oxo-ethanamine dihydrochloride:

1.40 g (3.25 mmol) of t-butyl 2-[4-(5H-dibenzo[a,d][7]annulen-5-ylidene)-1-piperidinyl]-2-oxoethylcarbamate was dissolved in 20 ml of 1,4-dioxane. 12 ml of 4 N hydrochloric acid / 1,4-dioxane solution was added to the obtained solution, and they were stirred overnight. After the neutralization with 4 N aqueous sodium hydroxide solution, the solvent was evaporated under reduced pressure. Saturated aqueous sodium chloride solution was added to the reaction mixture. After the extraction with ethyl acetate 3 times, the extract was dried over anhydrous sodium sulfate and then the solvent was evaporated under reduced pressure. 10 ml of a solution of ethyl acetate : hexane (1:2) and then 2 ml of 4 N hydrochloric acid / 1,4-dioxane solution were added to the residue. The resultant precipitates were taken by the filtration, washed with a solution of ethyl acetate : hexane (1:2) and air-dried. After further drying under reduced pressure, the title compound was obtained.

Yield: 1.15 g (3.06 mmol), 94 %

MS (ESI, m/z) 415 $(M+H+DMSO-d_6)^+$

^{1}H-NMR ($CDCl_3$) (free): 2.12-2.36 (4H, m), 2.36 (2H, s), 2.76-3.12 (2H, m), 3.13-3.50 (3H, m), 3.88-4.00 (1H, m), 6.92 (2H, s), 7.12-7.38 (8H, m).

Example 3

Synthesis of ethyl 2-[4-(5H-dibenzo[a,d][7]annulen-5-ylidene)-1-piperidinyl]-2-oxoethylcarbamate:

375 mg (1.00 mmol) of 2-[4-(5H-dibenzo[a,d][7]annulen-5-ylidene)-1-piperidinyl-2-oxoethanamine dihydrochloride was dissolved in 3 ml of dichloromethane. 303 mg (3.00 mmol) of triethylamine was added to the obtained solution. Then a solution of 130 mg (1.20 mmol) of ethyl chloroformate in 3 ml of dichloromethane was slowly added to the reaction mixture. After stirring overnight, saturated aqueous sodium hydrogencarbonate solution was added thereto. After extracting with ethyl acetate twice followed by drying under anhydrous sodium sulfate, the solvent was evaporated under reduced pressure. The residue was roughly purified by the silica gel chromatography (dichloromethane : methanol = 98 : 2) and then purified by the silica gel chromatography (hexane : ethyl acetate = 1:2) to obtain the title compound.

Yield: 213 mg (0.528 mmol), 53 %

MS (ESI, m/z) 403$(M+H)^+$

^{1}H-NMR ($CDCl_3$): 1.24 (3H, t), 2.12-2.36 (4H, m), 2.97-3.10 (2H, m), 3.38-3.50 (2H, m), 3.86-4.02 (3H, m), 4.13 (2H, q), 5.65 (1H, br s), 6.92 (2H, s), 7.14-7.20 (2H, m), 7.23-7.38 (6H, m).

Example 4

Synthesis of t-butyl (1S)-1-{[4-(5H-dibenzo[a,d]annulen-5-ylidene)-1-piperidinyl]carbonyl}-3-methylbutylcarbamate:

100 mg (0.366 mmol) of 4-(5H-dibenzo[a,d]annulen-5-ylidene)-1-piperidine, 109 mg (0.439 mmol) of N-t-butoxycarbonyl-(L)-leucine, 105 mg (0.549 mmol) of 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide hydrochloride and 5 mg (0.04 mmol) of 4-dimethylaminopyridine were dissolved in 2 ml of dichloromethane. 74 mg (0.73 mmol) of triethylamine was added to the obtained solution, and they were stirred overnight. Saturated aqueous sodium hydrogencarbonate solution was added to the obtained mixture. After extracting with ethyl acetate 3 times, the organic layer was washed with saturated aqueous sodium chloride solution. After drying over anhydrous sodium sulfate, the solvent was evaporated under reduced pressure, and the residue was purified by the silica gel chromatography (hexane : ethyl acetate = 84 : 16 to 75 : 25) to obtain the title compound.

Yield: 29.5 mg (0.065 mmol), 17 %

MS (ESI, m/z) 487$(M+H)^+$

^{1}H-NMR ($CDCl_3$): 0.84-0.99 (6H, m), 1.23-1.31 (2H, m), 1.41 (9H, d), 1.70 (1H, m), 2.10-2.40 (4H, m), 2.90-3.20 (2H, m), 3.61 (1H, m), 3.94 (1H, m), 4.62 (1H, m), 5.28 (1H, d), 6.92 (2H, d), 7.14-7.38 (8H, m).

Example 5

Synthesis of (1R)-N-{2-[4-(5H-dibenzo[a,d][7]annulen-5-ylidene)-1-piperidinyl]-2-oxoethyl}-2,2-dimethylcyclopropane carboxyamide:

200 mg (0.542 mmol) of 2-[4-(5H-dibenzo[a,d][7]annulen-5-ylidene)-1-piperidinyl]-2-oxoethanamine dihydrochloride was dissolved in 1.5 ml of dichloromethane. 137 mg (1.36 mmol) of triethylamine was added to the obtained solution. Then a solution of 86.1 mg (0.650 mmol) of (S)-2,2-dimethylcyclopropanecarboxylic acid chloride in 0.5 ml of dichloromethane was slowly added to the obtained mixture. After

stirring for 1 hour, the obtained mixture was roughly purified by the silica gel chromatography (dichloromethane : methanol = 98 : 2) and then purified by the silica gel chromatography (Chromatorex™ NH, Fuji Silysia Chemical LTD., hexane : ethyl acetate = 92:8 to 1:4) to obtain the title compound.

Yield: 154 mg (0.362 mmol), 67 %

MS (ESI, m/z) 427 $(M+H)^+$

^{1}H-NMR ($CDCl_3$): 0.73 (1H, m), 1.04-1.19 (7H, m), 1.36 (1H, m), 2.12-2.36 (4H, m), 2.96-3.12 (2H, m), 3.40-3.52 (1H, m), 3.80-4.16 (3H, m), 6.65 (1H, bs), 6.92 (2H, s), 7.13-7.20 (2H, m), 7.21-7.40 (6H, m).

Example 6

Synthesis of (1R)-N-{2-[4-(10,11-dihydro-5H-dibenzo[a,d][7]annulen-5-ylidene)-1-piperidinyl]-2-oxoethyl}-2,2-dimethylcyclopropane carboxyamide:

72.8 mg of palladium carbon (10 % w/v) was added to 72.8 mg (0.171 mmol) of (1R)-N-{2-[4-(5H-dibenzo[a,d][7]annulen-5-ylidene)-1-piperidinyl]-2-oxoethyl}-2,2-dimethylcyclopropanecarboxyamide in 10 ml of ethanol, and they were stirred at 4.0 MPa in hydrogen gas atmosphere overnight. After the filtration, the solvent was evaporated under reduced pressure to obtain the title compound.

Yield: 67.1 mg (0.157 mmol), 92 %

MS (ESI, m/z) 429$(M+H)^+$

^{1}H-NMR ($CDCl_3$): 0.75 (1H, dd), 1.05-1.41 (7H, m), 1.37 (1H, dd), 2.30-2.51 (4H, m), 2.35-2.82 (2H, m), 3.09-3.24 (2H, m), 3.31-3.46 (2H, m), 3.48-3.60 (1H, m), 4.00-4.19 (3H, m), 6.68 (1H, br s), 7.00-7.04 (2H, m), 7.04-7.18 (6H, m).

Example 8

Synthesis of N-{2-[4-(5H-dibenzo[a,d][7]annulen-5-ylidene)-1-piperidinyl]-2-oxoethyl}-2,2-dimethylpropanamide:

100 mg (0.271 mmol) of 2-[4-(5H-dibenzo[a,d][7]annulen-5-ylidene)-1-piperidinyl]-2-oxoethanamine dihydrochloride was dissolved in 1 ml of dichloromethane. 82.3 mg (0.813 mmol) of triethylamine was added to the obtained solution. A solution of 39.2 mg (0.325 mmol) of pivaloyl chloride in 0.5 ml of dichloromethane was slowly added to the obtained mixture. After stirring for 30 minutes, the obtained product was purified by the silica gel chromatography (hexane : ethyl acetate = 9:1 to 3:1).

Yield: 62.9 mg (0.152 mmol) (56 %)

MS (ESI, m/z) 415$(M+H)^+$

^{1}H-NMR ($CDCl_3$): 1.21 (9H, s), 2.14-2.35 (4H, m), 2.98-3.12 (2H, m), 3.40-3.53 (1H, m), 3.88-4.09 (3H, m), 6.83 (1H, br s), 6.92 (2H, s), 7.12-7.22 (2H, m), 7.22-7.40 (6H, m).

Example 9

Synthesis of N-(t-butyl)-4-[4-(5H-dibenzo[a,d][7]annulen-5-ylidene)-1-piperidinyl]-4-oxobutanamide:

100 mg (0.268 mmol) of 4-[4-(5H-dibenzo[a,d][7]annulen-5-ylidene)-1-piperidinyl]-4-oxobutanoic acid, 23.5 mg (0.321 mmol) of t-butylamine, 3 mg (0.03 mmol) of 4-dimethylaminopyridine and 77.1 mg (0.402 mmol) of 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide hydrochloride were dissolved in 1 ml of dichloromethane. 35.2 mg (0.348 mmol) of triethylamine was added to the obtained solution, and they were stirred overnight. The obtained product was purified by the silica gel chromatography (hexane : ethyl acetate = 2:1 to 4:6) to obtain the title compound.

Yield: 33.3 mg (0.078 mmol), 29 %

MS (ESI, m/z) 429 $(M+H)^+$

^{1}H-NMR ($CDCl_3$): 1.32 (9H, s), 2.08-2.36 (4H, m), 2.41 (2H, t), 2.50-2.71 (2H, m), 2.24-2.96 (2H, m), 3.58 (1H, m), 3.93 (1H, m), 5.77 (1H, br s), 6.92 (2H, s), 7.14-7.38 (8H, m).

Example 10

Synthesis of N-{2-[4-(5H-dibenzo[a,d][7]annulen-5-ylidene)-1-piperidinyl]-2-oxoethyl}-2-methyl-1-propanamine hydrochloride:

128.5 mg (0.264 mmol) of t-butyl 2-[4-(5H-dibenzo[a,d][7]annulen-5-ylidene)-1-piperidinyl]-2-oxoethyl(isobutyl)carbamate was dissolved in 1 ml of 1,4-dioxane. 0.5 ml of 4 N hydrochloric acid / 1,4-dioxane solution was added to the obtained solution, and they were stirred overnight. Saturated aqueous sodium hydrogencarbonate solution was added to the reaction mixture. After the extraction with ethyl acetate 3 times, the extract was dried over anhydrous sodium sulfate and then the solvent was evaporated under reduced pressure. The residue was purified by the silica gel chromatography (hexane : ethyl acetate = 89:11 to 65:35). The solvent was evaporated under reduced pressure, and the residue was dissolved in 2 ml of diethyl ether. 4 N hydrochloric acid / ethyl acetate solution was added to the obtained solution. The precipitates thus formed were taken by the filtration and then washed with diethyl ether. After drying under reduced pressure, the title compound was obtained.

Yield: 102.6 mg (0.242 mmol) 92 %

MS (ESI, m/z) 387 $(M+H)^+$

^{1}H-NMR ($CDCl_3$): 1.08 (6H, d), 2.10-2.40 (5h, m), 2.70-3.10 (4H, m), 3.41 (1H, br s), 3.69-4.10 (3H, m), 6.92 (2H, s), 7.10-7.21 (2H, m),

7.23-7.39 (6H, m), 9.03 (1H, br s), 9.68 (1H, br s).

Example 11

Synthesis of N-{3-[4-(5H-dibenzo[a,d][7]annulen-5-ylidene)-1-piperidinyl]-3-oxopropyl}-2,2-dimethylpropanamide:

Step 1

Synthesis of N-(2,2-dimethylpropanoyl)-β-alanine:

558 mg (4.03 mmol) of methyl 3-aminopropionate was dissolved in 20 ml of 1 N aqueous sodium hydroxide solution. 362 mg (3.00 mmol) of pivaloyl chloride was immediately added to the obtained solution, and they were stirred for 4 hours. 15 ml of 2 N aqueous hydrochloric acid was added to the reaction mixture. After extracting with ethyl acetate 3 times followed by drying under anhydrous sodium sulfate, the solvent was evaporated under reduced pressure to obtain the title compound.

Yield: 173 mg (0.929 mmol), 23 %

^{1}H-NMR ($CDCl_3$): 1.18 (9H, s), 2.60 (2H, t), 3.51 (2H, q), 6.34 (1H, br s).

Step 2

Synthesis of N-{3-[4-(5H-dibenzo[a,d][7]annulen-5-ylidene)-1-piperidinyl]-3-oxopropyl}-2,2-dimethylpropanamide:

275 mg (1.01 mmol) of [4-(5H-dibenzo[a,d][7]annulen-5-ylidene)-1-piperidine, 90.0 mg (0.480 mmol) of N-(2,2-dimethylpropanoyl)-β-alanine, 193 mg (1.01 mmol) of 1-ethyl-3-(3'-dimethylaminopropyl) carbodiimide hydrochloride and 6 mg (0.05 mmol) of 4-dimethylaminopyridine were dissolved in 3 ml of dichloromethane. 152 mg (1.50 mmol) of triethylamine was added to the obtained solution. After stirring for 3 hours, the obtained mixture was roughly purified by the silica gel chromatography (Chromatorex™ NH, Fuji Silysia Chemical LTD., hexane : ethyl acetate = 89:11 to 7:3) and then purified by the

silica gel chromatography (hexane : ethyl acetate = 2:3 to 1:4) to obtain the title compound.

Yield: 147 mg (0.343 mmol), 72 %

MS (ESI, m/z) 429 $(M+H)^+$

^{1}H-NMR ($CDCl_3$): 1.16 (9H, s), 2.11-2.36 (4H, m), 2.48 (2H, q), 2.94-3.12 (2H, m), 3.52 (3H, q), 3.84-4.00 (1H, m), 6.62 (1H, t), 6.92 (2H, s), 7.13-7.20 (2H, m), 7.22-7.38 (6H, m).

Example 12

Synthesis of N-{2-[4-(5H-dibenzo[a,d][7]annulen-5-ylidene)-1-piperidinyl]-2-oxoethyl}-3,3-dimethylbutanamide:

80.0 mg (0.217 mmol) of 2-[4-(5H-dibenzo[a,d][7]annulen-5-ylidene)-1-piperidinyl]-2-oxoethanamine dihydrochloride was dissolved in 1 ml of dichloromethane. 75.9 mg (0.750 mmol) of triethylamine was added to the obtained solution. Then a solution of 35.1 mg (0.260 mmol) of 3,3-dimethylbutanoyl chloride in 0.5 ml of dichloromethane was slowly added to the obtained mixture. After stirring for 30 minutes, the product was purified by the silica gel chromatography (hexane : ethyl acetate = 93:7 to 3:1) to obtain the title compound.

Yield: 80.1 mg (0.187 mmol), 86 %

MS (ESI, m/z) 429 $(M+H)^+$

^{1}H-NMR ($CDCl_3$): 1.03 (9H, s), 2.12 (2H, s), 2.15-2.39 (4H, m), 2.96-3.11 (2H, m), 3.40-3.54 (1H, m), 3.88-4.13 (3H, m), 6.49 (1H, br s), 6.92 (2H, s), 7.14-7.21 (2H, m), 7.21-7.41 (6H, m).

Example 13

Synthesis of isopropyl 2-[4-(5H-dibenzo[a,d][7]annulen-5-ylidene)-1-piperidinyl]-2-oxoethylcarbamate:

80.0 mg (0.217 mmol) of 2-[4-(5H-dibenzo[a,d][7]annulen-5-

ylidene)-1-piperidinyl]-2-oxoethanamine dihydrochloride was dissolved in 1 ml of dichloromethane. 75.9 mg (0.750 mmol) of triethylamine was added to the obtained solution. Then a solution of 31.9 mg (0.260 mmol) of isopropyl chloroformate in 0.5 ml of dichloromethane was slowly added to the obtained mixture. After stirring for 30 minutes, the obtained product was purified by the silica gel chromatography (hexane : ethyl acetate = 93:7 to 3:1) to obtain the title compound.

Yield: 38.6 mg (0.093 mmol), 43 %

MS (ESI, m/z) 417 $(M+H)^+$

^{1}H-NMR ($CDCl_3$): 1.23 (6H, d), 2.12-2.48 (4H, m), 2.92-3.11 (2H, m), 3.36-3.53 (1H, m), 3.83-4.09 (3H, m), 4.90 (1H, m), 5.59 (1H, br s), 6.92 (2H, s), 7.14-7.20 (2H, m), 7.23-7.38 (6H, m).

Example 14

Synthesis of N-{3-[4-(5H-dibenzo[a,d][7]annulen-5-ylidene)-1-piperidinyl]-3-oxopropyl}-2,2-dimethyl-1-propanamine hydrochloride:

5ml of 4 N hydrochloric acid / 1,4-dioxane solution was added to 184.1 mg (0.357 mmol) of t-butyl 3-[4-(5H-dibenzo[a,d][7]annulen-5-ylidene)-1-piperidinyl]-3-oxopropyl(neopentyl)carbamate, and they were stirred for 1 hour. The solvent was evaporated under reduced pressure. 5 ml of diethyl ether was added to the residue, and then 1 ml of 4 N hydrochloric acid / ethyl acetate solution was added thereto. The precipitates thus formed were taken by the filtration, washed with diethyl ether and dried under reduced pressure to obtain the title compound.

Yield: 149 mg (0.357 mmol), 100 %

MS (ESI, m/z) 415 $(M+H)^+$

^{1}H-NMR ($CDCl_3$): 1.24 (9H, s), 2.14-2.43 (4H, m), 2.52 (2H, s),

2.62-3.37 (6H, m), 3.52 (1H, m), 3.95 (1H, m), 6.92 (2H, s), 7.12-7.24 (2H, m), 7.26-7.40 (6H, m), 9.05 (1H, br s), 9.55 (1H, br s).

Example 15

Synthesis of N-((1S)-1-{[4-(5H-dibenzo[a,d]annulen-5-ylidene)-1-piperidinyl]-carbonyl}-3-methylbutyl)-1-azepanecarboxyamide:

100 mg (0.366 mmol) of 4-(5H-dibenzo[a,d][7]annulen-5-ylidene)-1-piperidine, 124 mg (0.439 mmol) of N-t-azepanecarboxyamido-(L)-leucine, 105 g (0.549 mmol) of 1-ethyl-3-(3'-dimethylaminopropyl) carbodiimide hydrochloride and 5 mg (0.04 mmol) of 4-dimethylamino pyridine were dissolved in 2 ml of dichloromethane. 74 mg (0.73 mmol) of triethylamine was added to the obtained solution, and they were stirred overnight. Saturated aqueous sodium hydrogencarbonate solution was added to the obtained mixture. After extracting with ethyl acetate 3 times, the organic layer was washed with saturated aqueous sodium chloride solution. After drying over anhydrous sodium sulfate, the solvent was evaporated under reduced pressure, and the residue was roughly purified by the silica gel chromatography (hexane : ethyl acetate = 4:1 to 65:35) and then purified by the silica gel chromatography (hexane : ethyl acetate = 3:1) to obtain the title compound.

Yield: 98.9 mg (0.194 mmol), 53 %

MS (ESI, m/z) 512 $(M+H)^+$

^{1}H-NMR ($CDCl_3$): 0.54-1.02 (6H, m), 1.23-1.82 (11H, m), 2.10-2.25 (4H, m), 3.00 (1H, m), 3.16 (1H, m), 3.39 (4H, m), 3.65 (1H, m), 3.3 (1H, m), 4.90 (1H, m), 5.21 (1H, m), 6.92 (2H, s), 7.15-7.39 (8H, m).

Example 16

Synthesis of t-butyl 2-[4-(10,11-dihydro-5H-dibenzo[a,d][7]annulen-5-

ylidene)-1-piperidinyl]-2-oxoethyl carbamate:

400 mg of palladium carbon (10 % w/v) was added to 400 mg (0.930 mmol) of t-butyl 2-[4-(5H-dibenzo[a,d][7]annulen-5-ylidene)-1-piperidinyl]-2-oxoethylcarbamate in 5 ml of ethanol, and they were stirred at 3.9 MPa in hydrogen gas atmosphere overnight. After the filtration, the solvent was evaporated under reduced pressure to obtain the title compound.

Yield: 397 g (0.918 mmol), 99 %

MS (ESI, m/z) 433 $(M+H)^+$

^{1}H-NMR ($CDCl_3$): 1.46 (9H, s), 2.29-2.50 (4H, m), 2.77-2.92 (2H, m), 3.08-3.21 (2H, m), 3.31-3.45 (2H, m), 3.45-3.56 (1H, m), 3.87-4.10 (3H, m), 5.56 (1H, br s), 7.00-7.07 (2H, m), 7.09-7.20 (6H, m).

Example 17

Synthesis of t-butyl 2-oxo-2-[4-(9H-thioxanthen-9-ylidene)-1-piperidinyl]ethylcarbamate:

500 mg (1.79 mmol) of 4-(9H-thioxanthen-9-ylidene)-1-piperidine and 515 mg (2.69 mmol) of 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide hydrochloride were suspended in 5 ml of dichloromethane. 415 mg (2.15 mmol) of N-t-butoxycarbonylglycine, 362 mg (3.58 mmol) of triethylamine and 22 mg (0.18 mmol) of 4-dimethylaminopyridine were added to the obtained suspension, and they were stirred overnight. Saturated aqueous sodium hydrogencarbonate solution was added to the obtained mixture. After extracting with ethyl acetate twice and drying over anhydrous sodium sulfate, the solvent was evaporated under reduced pressure, and the residue was roughly purified by the silica gel chromatography (dichloromethane : methanol = 98:2) and then purified by the thin-layer

silica gel chromatography (dichloromethane : methanol = 15:1) to obtain the title compound.

Yield: 43.1 mg (0.100 mmol), 5.6 %

MS (ESI, m/z) 437 $(M+H)^+$

^{1}H-NMR ($CDCl_3$): 1.45 (9H, s), 2.50-2.64 (2H, m), 2.68-2.81 (2H, m), 2.92-3.14 (2H, m), 3.52-3.62 (1H, m), 3.85-4.10 (2H, m), 4.13-4.24 (1H, m), 5.53 (1H, br s), 7.16-7.32 (6H, m), 7.48-7.54 (2H, d).

Example 18

Synthesis of ethyl 2-[4-(10,11-dihydro-5H-dibenzo[a,d][7]annulen-5-ylidene)-1-piperidinyl]-2-oxoethyl carbamate:

100 mg of palladium carbon (10 % w/v) was added to 105 mg (0.261 mmol) of ethyl 2-[4-(5H-dibenzo[a,d][7]annulen-5-ylidene)-1-piperidinyl]-2-oxoethylcarbamate in 3 ml of ethanol, and they were stirred at 3.6 MPa in hydrogen gas atmosphere overnight. After the filtration, the solvent was evaporated under reduced pressure to obtain the title compound.

Yield: 101.8 mg (0.252 mmol), 97 %

MS (ESI, m/z) 405 $(M+H)^+$

^{1}H-NMR ($CDCl_3$): 1.26 (3H, t), 2.30-2.52 (4H, m), 2.75-2.92 (2H, m), 3.08-3.23 (2H, m), 3.30-3.45 (2H, m), 3.45-3.58 (1H, m), 3.90-4.20 (5h, m), 5.68(1H, br s), 6.98-7.07 (2H, m), 7.07-7.21 (6H, m).

Example 19

Synthesis of ethyl 2-oxo-2-[4-(9H-thioxanthen-9-ylidene)-1-piperidinyl]ethylcarbamate:

Step 1

Synthesis of 2-[4-(9H-thioxanthen-9-ylidene)-1-piperidinyl]-2-oxoethanamine hydrochloride:

135 mg (0.297 mmol) of t-butyl 2-oxo-2-[4-(9H-thioxanthen-9-ylidene)-1-piperidinyl]ethylcarbamate was dissolved in 2 ml of dioxane. After adding 2 ml of 4 N hydrochloric acid / 1,4-dioxane solution, they were stirred overnight. The obtained mixture was neutralized with saturated aqueous sodium hydrogencarbonate solution. After extracting with ethyl acetate twice and drying over anhydrous sodium sulfate, the solvent was evaporated under reduced pressure. 2 ml of dichloromethane and then 2 ml of 4 N hydrochloric acid / 1,4-dioxane solution were added to the residue. The resultant precipitates were taken by the filtration, washed with dichloromethane and air-dried. After further drying under reduced pressure, the title compound was obtained.

Yield: 72.4 mg (0.195 mmol), 66 %

^{1}H-NMR (DMSO-d_6): 2.40-2.54 (2H, m), 2.57-2.80 (2H, m), 3.20 (2H, m), 3.34-3.75 (1H, m), 3.80-3.96 (3H, m), 7.22-7.48 (6H, m), 7.57 (2H, d), 8.16 (3H, br s).

Step 2

Synthesis of ethyl 2-oxo-2-[4-(9H-thioxanthen-9-ylidene)-1-piperidinyl]ethylcarbamate:

50 mg (0.134 mmol) of 2-[4-(9H-thioxanthen-9-ylidene)-1-piperidinyl]-2-oxoethanamine hydrochloride was dissolved in dichloroethane. 41 mg (0.405 mmol) of triethylamine was added to the obtained solution. A solution of 17.5 mg (0.161 mmol) of ethyl chloroformate in 0.5 ml of dichloromethane was added to the resultant mixture. After stirring for 15 minutes, the product was purified by the thin-layer silica gel chromatography (hexane : ethyl acetate = 85:100) to obtain the title compound.

Yield: 36.7 mg (0.0897 mmol), 67 %

MS (ESI, m/z) 409 $(M+H)^+$

^{1}H-NMR ($CDCl_3$): 1.26 (3H, t), 2.48-2.64 (2H, m), 2.68-2.82 (2H, m), 2.92-3.16 (2H, m), 3.51-3.64 (1H, m), 3.90-4.24 (5h, m), 5.67 (1H, br s), 7.22-7.33 (6H, m), 7.51 (2H, d).

Example 20

Synthesis of t-butyl 3-[4-(5H-dibenzo[a,d][7]annulen-5-ylidene)-1-piperidinyl]-3-oxopropylcarbamate:

50 mg (0.183 mmol) of 4-(5H-dibenzo[a,d][7]annulen-5-ylidene)-1-piperidine was dissolved in 1 ml of dichloromethane. 41.5 mg (0.219 mmol) of N-t-butoxycarbonyl-3-aminopropionic acid, 2 mg (0.018 mmol) of 4-dimethylaminopyridine, 37 mg (0.366 mmol) of triethylamine and 52.6 mg (0.274 mmol) of 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide hydrochloride were added to the obtained solution, and they were stirred overnight. After the purification by the thin-layer silica gel chromatography (hexane : ethyl acetate = 2:3), the title compound was obtained.

Yield: 72.3 mg (0.163 mmol), 89 %

MS (ESI, m/z) 445 $(M+H)^+$

^{1}H-NMR ($CDCl_3$): 1,49 (3H, s), 2.12-2.36 (4H, m), 3.86-3.36 (4H, m), 3.52-3.28 (1H, m), 3.85-4.08 (1H, m), 4.40-4.58 (1H, d), 4.69-4.83 (1H, d), 5.16 (1H, br s), 6.92 (2H, s), 7.13-7.22 (2H, m), 7.22-7.39 (6H, m).

Example 21

Synthesis of t-butyl (4S)-4-{[4-(5H-dibenzo[a,d][7]annulen-5-ylidene)-1-piperidinyl]carbonyl}-1,3-thiazolidine-3-carboxylate:

The reaction and the purification were conducted in the same manner as that of Example 20 except that N-t-butoxycarbonyl-3-

aminopropionic acid was replaced with 3-(t-butoxycarbonyl)-1,3-thiazolidine-4-carboxyilc acid.

Yield: 70.8 mg (0.145 mmol), 79 %

MS (ESI, m/z) 489 $(M+H)^+$

^{1}H-NMR ($CDCl_3$): 1.29-1.52 (9H, m), 2.10-2.50 (4H, m), 2.70-3.45 (4H, m), 3.51-3.76 (1H, m), 3.82-4.07 (1H, m), 4.47 (1H, d), 4.75 (1H, d), 4.82-5.23 (1H, m), 6.92 (2H, s), 7.17 (2H, d), 7.20-7.40 (6H, m).

Example 22

Synthesis of t-butyl (2R)-2-{[4-(5H-dibenzo[a,d][7]annulen-5-ylidene)-1-piperidinyl]carbonyl}-1-pyrrolidinecarboxylate:

100 mg (0.366 mmol) of 4-(5H-dibenzo[a,d][7]annulen-5-ylidene)-1-piperidine, 94.0 mg (0.439 mmol) of N-t-butoxycarbonyl-(L)-proline, 4 mg (0.036 mmol) of 4-dimethylaminopyridine and 105.2 mg (0.548 mmol) of 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide hydrochloride were dissolved in 1 ml of dichloromethane. 74 mg (0.731 mmol) of triethylamine was added to the obtained solution, and they were stirred for 3 hours. After the purification by the silica gel chromatography (hexane : ethyl acetate = 1:1), the title compound was obtained.

Yield: 155.8 mg (0.331 mmol), 91%

MS (ESI, m/z) 471$(M+H)^+$

^{1}H-NMR ($CDCl_3$): 1.26-1.52 (9H, m), 1.60-2.53 (8H, m), 2.80-3.26 (2H, m), 3.28-3.71 (3H, m), 3.77-4.10 (1H, m), 4.46-4.72 (1H, m), 6.92 (2H, s), 7.11-7.40 (8H, m).

Example 23

Synthesis of t-butyl 2-[3-(10,11-dihydro-5H-dibenzo[a,d][7]annulen-5-ylidene)-1-pyrrolidinyl]-2-oxoethylcarbamate:

94.0 mg (0.36 mmol) of 3-(10,11-dihydro-5H-dibenzo[a,d][7]-

annulen-5-ylidene)-1-pyrrolidine, 83.7 ml (0.44 mmol) of N-t-butoxycarbonylglycine, 103.8 mg (0.54 mmol) of 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide hydrochloride and 4.4 mg (0.04 mmol) of 4-dimethylaminopyridine were dissolved in 1 ml of dichloromethane. 72.8 mg (0.72 mmol) of triethylamine was added to the obtained solution. They were stirred overnight and then purified by the silica gel chromatography (hexane : ethyl acetate = 88:12 to 5:1) to obtain the title compound.

Yield: 97.9 g (0.217 mmol), 72 %

MS (ESI, m/z) 419 $(M+H)^+$

^{1}H-NMR ($CDCl_3$): 1.43 (9H, s), 2.48-2.67 (1H, m), 2.70-3.00 (3H, m), 3.20-3.39 (3H, m), 3.58-4.00 (4H, m), 4.30 (1H, t), 5.45 (1H, br s), 7.00-7.24 (8H, m).

Example 24

Synthesis of t-butyl 2-(4-dibenzo[b,e]thiepin-11(6H)-ylidene-1-piperidinyl)-2-oxoethylcarbamate:

88.0 mg (0.30 mmol) of 4-dibenzo[b,e]thiepin-11(6H)-ylidene-1-piperidine, 69.6 mg (0.36 mmol) of N-t-butoxycarbonylglycine, 86.3 g (0.45 mmol) of 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide hydrochloride and 3.7 mg (0.03 mmol) of 4-dimethylaminopyridine were dissolved in 1 ml of dichloromethane. 60.7 mg (0.60 mmol) of triethylamine was added to the obtained solution. They were stirred overnight and then purified by the silica gel chromatography (hexane : ethyl acetate = 88:12 to 5:1) to obtain the title compound.

Yield: 115.8 g (0.257 mmol), 86 %

MS (ESI, m/z) 451 $(M+H)^+$

^{1}H-NMR ($CDCl_3$): 1.45 (9H, s), 2.09-2.20 (2H, m), 2.38-2.61 (2H, m),

3.10-3.52 (4H, m), 3.34-4.08 (3H, m), 4.86 (1H, d), 5.52 (1H, br s), 6.96-7.16 (5 h, m), 7.20-7.35 (3H, m).

Example 25

Synthesis of 2-[4-(5H-dibenzo[a,d][7]annulen-5-ylidene)-1- piperidinyl]-2-oxoethylformamide:

150 mg (0.406 mmol) of 2-[4-(5H-dibenzo[a,d][7]annulen-5-ylidene)-1-piperidinyl]-2-oxoethanamine dihydrochloride, 80.5 mg (0.406 mmol) of 2,2-dimethyl-1-iodopropane and 84.3 mg (0.610 mmol) of potassium carbonate were dissolved in 1 ml of N,N-dimethylformamide, and the obtained solution was stirred at 120°C overnight. The product was purified by the silica gel chromatography (hexane : ethyl acetate = 9:1 to 2:3) to obtain the title compound.

Yield: 18.8 mg (0.052 mmol), 13 %

MS (ESI, m/z) 359 $(M+H)^+$

^{1}H-NMR ($CDCl_3$): 2.14-2.38 (4H, m), 2.96-3.12 (2H, m), 3.40-3.52 (1H, m), 3.88-4.18 (3H, m), 6.76 (1H, br s), 6.93 (2H, s), 7.10-7.42 (8H, m), 8.25 (1H, s).

Example 26

Synthesis of t-butyl 2-[4-(5H-dibenzo[a,d][7]annulen-5-ylidene)-1-piperidinyl]-2-oxoethyl(isobutyl)carbamate:

Step 1:

Synthesis of N-(t-butoxycarbonyl)-N-isobutylglycine:

366 mg (5.01 mmol) of isobutylamine and 1.52 g (15.0 mmol) of triethylamine were dissolved in 10 ml of water. 695 mg (5.00 mmol) of bromoacetic acid was added to the obtained solution, and they were stirred for 1 hour. A solution of 1.63 g (7.50 mmol) of di(t-butyl) dicarbonate in 5 ml of 1,4-dioxane was added to the resultant mixture,

and they were stirred for additional 1 hour. 10 ml of 1 N aqueous sodium hydroxide solution was added to the reaction mixture. After extracting with dichloromethane twice, 11 ml of 1 N aqueous hydrochloric acid solution was added to the aqueous layer. After extracting with dichloromethane 3 times, the obtained organic layer was dried over anhydrous sodium sulfate and then the solvent was evaporated under reduced pressure to obtain the title compound.

Yield: 829.1 mg (3.58 mmol), 72 %

^{1}H-NMR ($CDCl_3$): 0.89 (6H, d), 1.45 (9H, d), 1.83 (1H, m), 3.09 (2H, t), 3.93 (2H, d).

Step 2:

Synthesis of t-butyl 2-[4-(5H-dibenzo[a,d][7]annulen-5-ylidene)-1-piperidinyl]-2-oxoethyl(isobutyl)carbamate:

178 mg (0.768 mmol) of N-(t-butoxycarbonyl)-N-isobutylglycine, 150 mg (0.549 mmol) of 4-(5H-dibenzo[a,d]annulen-5-ylidene) -1-piperidine, 210 mg (1.10 mmol) of 1-ethyl-3-(3'-dimethylaminopropyl) carbodiimide hydrochloride and 6 mg (0.05 mmol) of 4-dimethylamino pyridine were dissolved in 2 ml of dichloromethane. 139 mg (1.37 mmol) of triethylamine was added to the resultant solution and they were stirred for 1 hour. After the purification by the silica gel chromatography (hexane : ethyl acetate = 95:5 to 4:1), the title compound was obtained.

Yield: 222.1 mg (0.456 mmol) (83 %)

MS (ESI, m/z) 487 $(M+H)^+$

^{1}H-NMR ($CDCl_3$): 0.87 (6H, d), 1.44 (9H, d), 1.85 (1H, m), 2.10-2.48 (4H, m), 3.42-3.40 (4H, m), 3.49 (1H, br s), 3.72-4.34 (3H, m), 6.92 (2H, s), 7.12-7.38 (8H, m).

Example 27

Synthesis of t-butyl 2-[4-(5H-dibenzo[a,d][7]annulen-5-ylidene)-1-piperidinyl]-2-oxoethyl(methyl)carbamate:

83.1 mg (0.439 mmol) of N-(t-butoxycarbonyl)-N-methylglycine, 100 mg (0.366 mmol) of 4-(5H-dibeno[a,d]annulen-5-ylidene)-1-piperidine, 105 mg (0.549 mmol) of 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide hydrochloride and 5 mg (0.04 mmol) of 4-dimethylaminopyridine were dissolved in 1.5 ml of dichloromethane. 74.0 mg (0.732 mmol) of triethylamine was added to the resultant solution and they were stirred for 1 hour. After the purification by the silica gel chromatography (hexane : ethyl acetate = 89:11 to 65:35), the title compound was obtained.

Yield: 102 mg (0.229 mmol) (63 %)

MS (ESI, m/z) 445 $(M+H)^+$

^{1}H-NMR ($CDCl_3$): 1.45 (9H, d), 2.12-2.37 (4H, m), 2.91 (3H, s), 2.95-3.12 (2H, m), 3.49 (1H, br s), 3.82-4.18 (3H, m), 6.93 (2H, s), 7.14-7.36 (8H, m).

Example 28

Synthesis of N-(t-butyl)-N'-{2-[4-(5H-dibenzo[a,d][7]annulen-5-ylidene)-1-piperidinyl]-2-oxoethyl}urea:

89.2 mg (0.55 mmol) of 1,1'-carbonylbis-1H-imidazole and 25.3 mg (0.25 mmol) of triethylamine were dissolved in 2.5 ml of tetrahydrofuran. A solution of 36.6 mg (0.50 mmol) of t-butylamine in 1 ml of tetrahydrofuran was slowly added to the resultant solution at 0°C in argon stream. After stirring for 1 hour, a solution of 110.7 mg (0.30 mmol) of 2-[4-(5H-dibenzo[a,d][7]annulen-5-ylidene)-1-piperidinyl]-2-oxoethanamine dihydrochloride and 30.3 mg (0.30 mmol) of

triethylamine in 1 ml of tetrahydrofuran was slowly added thereto. After stirring for 2 hours, the solvent was evaporated and the product was purified by the silica gel chromatography (hexane : ethyl acetate = 85:15 to 3:2) to obtain the title compound.

Yield: 70.7 mg (0.165 mmol), 66 %

MS (ESI, m/z) 430$(M+H)^+$

^{1}H-NMR ($CDCl_3$): 1.31 (9H, s), 2.10-2.35 (4H, m), 2.03-3.10 (2H, m), 3.40-3.52 (1H, m), 3.84-4.10 (3H, m), 4.56 (1H, br s), 5.30 (1H, s), 6.92 (2H, s), 7.14-7.24 (2H, m), 7.27-7.7.27 (6H, m).

Example 29

Synthesis of t-butyl 2-({2-[4-(5H-dibenzo[a,d][7]annulen-5-ylidene)-1-piperidinyl]-2-oxoethyl}amino)-2-oxoethylcarbamate:

35.0 mg (0.095 mmol) of 2-[4-(5H-dibenzo[a,d][7]annulen-5-ylidene)-1-piperidinyl]-2-oxoethanamine dihydrochloride, 19.7 mg (0.114 mmol) of N-t-butoxycarbonylglycine, 27.2 mg (0.142 mmol) of 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide hydrochloride and 1 mg (0.01 mmol) of 4-dimethylaminopyridine were dissolved in 1 ml of dichloromethane. 19.2 mg (0.190 mmol) of triethylamine was added to the obtained solution, and they were stirred for 1 hour. The product was purified by the silica gel chromatography (hexane : ethyl acetate = 7:3 to 3:7) to obtain the title compound.

Yield: 31.8 mg (0.065 mmol), 69 %

MS (ESI, m/z) 488 $(M+H)^+$

^{1}H-NMR ($CDCl_3$): 1.45 (9H, s), 2.12-2.38 (4H, m), 2.94-3.11 (2H, m), 3.38-3.52 (2H, m), 3.85 (2H, d), 3.91-4.10 (3H, m), 5.06 (1H, br s), 6.92 (2H, s), 7.00 (1H, br s), 7.13-7.22 (2H, m), 7.22-7.39 (6H, m).

Example 30

Synthesis of t-butyl 3-({2-[4-(5H-dibenzo[a,d][7]annulen-5-ylidene)-1-piperidinyl]-2-oxoethyl}amino)-3-oxopropylcarbamate:

35.0 mg (0.095 mmol) of 2-[4-(5H-dibenzo[a,d][7]annulen-5-ylidene)-1-piperidinyl]-2-oxoethanamine dihydrochloride, 21.5 mg (0.114 mmol) of N-t-butoxycarbonylalanine, 27.2 mg (0.142 mmol) of 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide hydrochloride and 1 mg (0.01 mmol) of 4-dimethylaminopyridine were dissolved in 1 ml of dichloromethane. 19.2 mg (0.190 mmol) of triethylamine was added to the obtained solution, and they were stirred for 1 hour. The product was purified by the silica gel chromatography (hexane : ethyl acetate = 7:3 to 3:7) to obtain the title compound.

Yield: 32.5 mg (0.065 mmol), 68 %

MS (ESI, m/z) 502 $(M+H)^+$

^{1}H-NMR ($CDCl_3$): 1.42 (9H, s), 2.12-2.38 (4H, m), 2.45 (2H, t), 3.04 (2H, m), 3.32-3.51 (3H, m), 3.87-4.10 (3H, m), 5.14 (1H, br s), 6.59 (1H, br s), 6.92 (2H, s), 7.13-7.40 (8H, m).

Example 31

Synthesis of t-butyl 3-[4-(5H-dibenzo[a,d][7]annulen-5-ylidene)-1-piperidinyl]-3-oxopropyl(neopentyl)carbamate:

872 mg (10.0 mmol) of 2,2-dimethylpropylamine was dissolved in 10 ml of ethanol. 34.0 mg (0.50 mmol) of sodium ethoxide and 1.00 g (10.0 mmol) of ethylacrylic acid were added to the obtained solution, and they were stirred overnight. 1 ml of water was added to the reaction mixture and the organic solvent was evaporated under reduced pressure. 2.62 g (12.0 mmol) of di(t-butyl) dicarbonate and 25 ml of 1 N aqueous sodium hydroxide solution were added to the residue, and they were stirred for 3.5 hours. After extracting with dichloromethane twice, the

aqueous layer was neutralized with 1 N aqueous hydrochloric acid solution. After extracting with dichloromethane 3 times, the extract was dried over anhydrous sodium sulfate and then the solvent was evaporated under reduced pressure. The obtained product was dissolved in 2 ml of dichloromethane. 145 mg (0.531 mmol) of 4-(5H-dibenzo[a,d][7]annulen-5-ylidene)-1-piperidine, 122 mg (0.637 mmol) of 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide hydrochloride and 6 mg (0.05 mmol) of 4-dimethylaminopyridine were added to the obtained solution. 107.5 mg (1.06 mmol) of triethylamine was further added to the reaction mixture, and they were stirred for 2 hour. The product was purified by the silica gel chromatography (hexane : ethyl acetate = 89:11 to 4:1) to obtain the title compound.

Yield: 233 mg (0.452 mmol), 85 %

MS (ESI, m/z) 515 $(M+H)^+$

^{1}H-NMR ($CDCl_3$): 0.91 (9H, s), 1.43 (9H, s), 2.10-2.40 (4H, m), 2.48-2.71 (2H, m), 2.94-3.21 (4H, m), 3,49 (2H, t), 3.62 (1H, m), 3.85-3.98 (1H, m), 6.92 (2H, s), 7.14-7.23 (2H, m), 7.23-7.38 (6H, m).

Example 32

Synthesis of t-butyl 2-[4-(10,11-dihydro-5H-dibenzo[b,f]azepin-5-yl)-1-piperidinyl]-2-oxoethylcarbamate:

60.0 mg (0.216 mmol) of 5-(4-piperidinyl)-10,11-dihydro-5H-dibenzo-[b,f]azepine, 50.0 mg (0.258 mmol) of N-t-butoxycarbonylglycine, 62.1 mg (0.324 mmol) of 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide hydrochloride and 3 mg (0.03 mmol) of 4-dimethylaminopyridine were dissolved in 1 ml of dichloromethane. 43.7 mg (0.432 mmol) of triethylamine was added to the obtained solution, and they were stirred for 1 hour. The product was purified by the silica gel chromatography

(hexane : ethyl acetate = 89:11 to 65:35) to obtain the title compound.

Yield: 81.1 mg (0.186 mmol), 86 %

MS (ESI, m/z) 436 $(M+H)^+$

^{1}H-NMR ($CDCl_3$): 1.43 (9H, s), 1.60-1.77 (2H, m), 1.98-2.10 (2H, m), 2.77 (2H, br s), 3.15 (1H, m), 3.28 (1H, m), 3.38-3.60 (3H, m), 3.80-4.02 (3H, m), 4.20 (1H, m), 5.50(1H, br s), 6.93-7.00 (2H, m), 7.05-7.15 (6H, m).

Example 33

Synthesis of t-butyl (1S)-1-{[4-(5H-dibenzo[a,d][7]annulen-5-ylidene)-1-piperidinyl]carbonyl}-3-methylbutyl(methyl)carbamate:

389 mg (1.59 mmol) of t-butoxycarbonyl-N-methyl-L-leucine, 311 mg (1.62 mmol) of 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide hydrochloride, 416 mg (1.52 mmol) of 4-(5H-dibenzo[a,d][7]annulen-5-ylidene)-1-piperidine and 0.22 ml (1.59 mmol) of triethylamine were stirred at room temperature overnight. Saturated aqueous sodium hydrogencarbonate solution was added to the reaction mixture. After extracting with dichloromethane, the organic layer was dried over anhydrous sodium sulfate and then concentrated under reduced pressure. The residue was purified by the silica gel chromatography (hexane : ethyl acetate = 3:1) to obtain the title compound.

Yield: 368 mg (0.74 mmol), 48 %

MS (ESI, m/z) 501 $(M+H)^+$

^{1}H-NMR ($CDCl_3$): 0.86-0.98 (6H, dd), 1.34-1.65 (10H, m), 2.03-2.38 (4H, m), 2.64-2.84 (3H, m), 2.88-4.18 (6H, m), 4.78-5.12 (1H, m), 6.90-6.94 (2H, m), 7.11-7.38 (8H, m).

Example 34

Synthesis of N-((1S)-1-{[4-(5H-dibenzo[a,d][7]annulen-5-ylidene)-1-

piperidinyl]carbonyl}-3-methylbutyl)-N-methylamine hydrochloride:

344 mg (0.69 mmol) of t-butyl (1S)-1-{[4-(5H-dibenzo[a,d][7] annulen-5-ylidene)-1-piperidinyl]carbonyl}-3-methylbutyl(methyl)carbam ate was dissolved in 2 ml of 1,4-dioxane. 4 ml of 4 N hydrochloric acid / 1,4-dioxane solution was added to the obtained solution, and they were stirred at room temperature for 5 hours and then concentrated under reduced pressure to obtain the title compound.

Yield: 301 mg (0.69 mmol), 100 %

MS (ESI, m/z) 401 $(M+H)^+$

^{1}H-NMR ($CDCl_3$) : 0.86-1.04 (6H, m), 1.66-2.01 (5 H, m), 2.16-2.56 (4H, m), 2.72 (3H, d), 2.94-3.26 (2H, m), 3.54-3.72 (1H, m), 3.94-4.08 (1H, m), 4.24-4.35 (1H, m), 6.89-6.93 (2H, m), 7.14-7.20 (2H, m), 7.22-7.38 (6H, m).

Example 35

Synthesis of t-butyl 2-[[3-(5H-dibenzo[a,d][7]annulen-5-yl)propyl] (methyl)-amino]-2-oxoethylcarbamate:

134 mg (0.70 mmol) of 1-ethyl-3-(3'-dimethylaminopropyl) carbodiimide hydrochloride, 176 mg (0.59 mmol) of protriptyline hydrochloride and 0.176 ml (1.26 mmol) of triethylamine were added to 129 mg (0.74 mmol) of t-butoxycarbonylglydine in 5 ml of dichloromethane, and they were stirred at room temperature overnight. Saturated aqueous sodium hydrogencarbonate solution was added to the reaction mixture. After extracting with dichloromethane, the organic layer was dried over anhydrous sodium sulfate and then concentrated under reduced pressure. The residue was purified by the silica gel chromatography (hexane : ethyl acetate = 3:1) to obtain the title compound.

Yield: 228 mg (0.54 mmol), 92 %

MS (ESI, m/z) 421 $(M+H)^+$

^{1}H-NMR ($CDCl_3$): 1.13-1.30 (2H, m), 1.44 (9H, s), 1.64-1.76 (2H, m), 2.73 (3H, d), 3.27-3.42 (1H, m), 4.36 (1H, s), 5.31 (1H, s), 5.98 (1H, s), 6.49 (2H, s), 7.29-7.50 (8H, m).

Example 36

Synthesis of t-butyl 2-[[3-(5H-dibenzo[a,d][7]annulen-5-ylidene)propyl]-(methyl)amino]-2-oxoethylcarbamate:

Step 1

Synthesis of 3-(5H-dibenzo[a,d][7]annulen-5-ylidene)-N-methyl-1-propanamine:

20 ml of saturated aqueous sodium hydrogencarbonate solution was added to 2.467 g (7.91 mmol) of cyclobenzaprine hydrochloride in 20 ml of chloroform, and they were stirred at room temperature for 10 minutes. After extracting with chloroform, the organic layer was dried over anhydrous sodium sulfate and then concentrated under reduced pressure. 15 ml of toluene was added to the residue, and they were heated at 80°C. 4.0 ml (41.8 mmol) of ethyl chloroformate was added thereto, and they were stirred at 80°C overnight. 4.0 ml (41.8 mmol) of ethyl chloroformate was added to the reaction mixture, and they were stirred under heating for 2 days. Water was added to the reaction mixture. After extracting with ethyl acetate, the organic layer was dried over anhydrous sodium sulfate and then concentrated under reduced pressure. The residue was purified by the silica gel chromatography (hexane : ethyl acetate = 1:1). 11.4 ml of 1-butanol and 1.97 g (35.1 mmol) of powdery potassium hydroxide were added to the obtained product, and they were stirred under heating at 120°C for 4

hours. The reaction mixture was poured in water at room temperature. After the extraction with chloroform, the organic layer was dried over anhydrous sodium sulfate and then concentrated under reduce pressure to obtain the title compound.

Yield: 1.725 g (6.60 mmol), 83 %

MS (ESI, m/z) 262 $(M+H)^+$

^{1}H-NMR ($CDCl_3$): 2.26-2.35 (2H, m), 2.30 (3H, s), 2.53-2.66 (2H, m), 5.53 (1H, t), 6.86 (2H, d), 7.21-7.37 (8H, m).

Step 2

Synthesis of t-butyl 2-[[3-(5H-dibenzo[a,d][7]annulen-5-ylidene)propyl]-(methyl)amino]-2-oxoethylcarbamate:

105 mg (0.60 mmol) of t-butoxycarbonylglycine, 111 mg (0.58 mmol) of 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide hydrochloride, 133 mg (0.51 mmol) of 3-(5H-dibenzo[a,d][7]annulen-5-ylidene)-N-methyl-1-propanamine and 0.08 ml (0.57 mmol) of triethylamine were stirred in 5 ml of dichloromethane at room temperature overnight. Saturated aqueous sodium hydrogencarbonate solution was added to the reaction mixture. After extracting with dichloromethane, the organic layer was dried over anhydrous sodium sulfate and then concentrated under reduced pressure. The residue was purified by the silica gel chromatography (hexane : ethyl acetate = 2:1) to obtain the title compound.

Yield: 130 mg (0.31 mmol), 61 %

MS (ESI, m/z) 419 $(M+H)^+$

^{1}H-NMR ($CDCl_3$): 1.45 (9H, d), 2.23-2.52 (2H, m), 2.68 (3H, d), 3.10-3.58 (2H, m), 3.72-3.88 (2H, m), 5.40-5.53 (2H, m), 6.84-6.88 (2H, m), 7.15-7.40 (8H, m).

Example 37

Synthesis of t-butyl (1S)-1-{[[3-(5H-dibenzo[a,d][7]annulen-5-ylidene) propyl]-(methyl)amino]carbonyl}-3-methylbutyl(methyl)carbamate:

280 mg (1.14 mmol) of t-butoxycarbonyl-N-methyl-L-leucine, 204 mg (1.06 mmol) of 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide hydrochloride, 271 mg (1.04 mmol) of 3-(5H-dibenzo[a,d][7]annulen-5-ylidene)-N-methyl-1-propanamine and 0.15 ml (1.08 mmol) of triethylamine were stirred in 10 ml of dichloromethane at room temperature overnight. Saturated aqueous sodium hydrogencarbonate solution was added to the reaction mixture. After extracting with dichloromethane, the organic layer was dried over anhydrous sodium sulfate and then concentrated under reduced pressure. The residue was purified by the silica gel chromatography (hexane : ethyl acetate = 82:18) to obtain the title compound.

Yield: 178 mg (0.37 mmol), 35 %

MS (ESI, m/z) 489 $(M+H)^+$

^{1}H-NMR ($CDCl_3$): 0.63-0.96 (6H, m), 1.24-1.62 (11H, m), 2.22-2.91 (9H, m), 3.10-3.70 (2H, m), 4.66-5.08 (1H, m), 5.41-5.58 (1H, m), 6.79-6.91 (2H, m), 7.16-7.38 (8H, m).

Example 38

Synthesis of (2S)-N-[3-(5H-dibenzo[a,d][7]annulen-5-ylidene)propyl]-N,4-dimethyl-2-(methylamino)pentanamide hydrochloride:

5 ml of dichloromethane and 2.5 ml of trifluoroacetic acid were added to 169 mg (0.35 mmol) of t-butyl (1S)-1-{[[3-(5H-dibenzo[a,d][7] annulen-5-ylidene)propyl](methyl)amino]carbonyl}-3-methylbutyl(methyl)carbamate, and they were stirred at room temperature for 2 hours. The reaction mixture was concentrated under reduced pressure. 1 N

aqueous sodium hydroxide solution was added thereto to make it basic. After extracting with ethyl acetate, the organic layer was dried over anhydrous sodium sulfate and then concentrated under reduced pressure. The residue was dissolved in 5 ml of 1,4-dioxane. 4 N hydrochloric acid / 1,4-dioxane solution was added to the obtained solution. The resultant mixture was concentrated under reduced pressure to obtain the title compound.

Yield: 145 mg (0.34 mmol) 99 %

MS (ESI, m/z) 389 $(M+H)^+$

^{1}H-NMR ($CDCl_3$): 0.74-0.94 (6H, m), 1.40-1.75 (2H, m), 2.06-2.83 (9H, m), 3.08-3.60 (2H, m), 3.75-4.11 (1H, m), 5.40-5.51 (1H, m), 6.77-6.92 (2H, m), 7.16-7.41 (8H, m).

Example 39

Synthesis of t-butyl 2-[[3-(10,11-dihydro-5H-dibenzo[a,d][7]annulen-5-ylidene)propyl](methyl)amino]-2-oxoethylcarbamate:

281 mg (1.47 mmol) of 1-ethyl-3-(3'-dimethylaminopropyl) carbodiimide hydrochloride, 281 mg (1.47 mmol) of nortriptyline hydrochloride and 0.40 ml (2.87 mmol) of triethylamine were added to 251 mg (1.44 mmol) of t-butoxycarbonylglycine in 10 ml of dichloromethane, and they were stirred at room temperature overnight. Saturated aqueous sodium hydrogencarbonate solution was added to the reaction mixture. After extracting with dichloromethane, the organic layer was dried over anhydrous sodium sulfate and then concentrated under reduced pressure. The residue was purified by the silica gel chromatography (hexane : ethyl acetate = 4:1) to obtain the title compound.

Yield: 203 mg (0.48 mmol), 33 %

MS (ESI, m/z) 421 $(M+H)^+$

^{1}H-NMR ($CDCl_3$): 1.44 (9H, s), 1.64-1.76 (2H, m), 2.30-2.48 (2H, m), 2.77 (3H, d), 2.85-3.56 (6H, m), 3.83-3.95 (2H, m), 5.43-5.75 (1H, brd), 5.79 (1H, dt), 7.00-7.28 (8H, m).

Example 40

Synthesis of t-butyl 2-[(5H-dibenzo[a,d][7]annulen-5-ylidenacetyl)amino] -ethylcarbamate:

Step 1

Synthesis of 5H-dibenzo[a,d][7]annulen-5-ylidenacetic acid:

890 mg (22.3 mmol) of sodium hydride (60 % oily) was added to 4.99 g (22.3 mmol) of ethyl diethylphosphonoacetate in 55 ml of dimethyl sulfoxide, and they were stirred at room temperature overnight. 4.58 g (22.2 mmol) of 5H-dibenzo[a,d]-5-cycloheptenone was added to the reaction mixture, and they were stirred at room temperature for 1 hour 15 minutes and then stirred under heating at 100°C for 2 days. Dimethyl sulfoxide was evaporated under reduced pressure. 20 ml of ethanol and 20 ml of 6 N aqueous sodium hydroxide solution were added to the residue, and they were stirred under heating at 100°C for 3 days. The reaction mixture was concentrated under reduced pressure and then acidified with 1 N hydrochloric acid. After extracting with ethyl acetate, the organic layer was dried over anhydrous sodium sulfate and then concentrated under reduced pressure. The residue was purified by the silica gel chromatography (hexane : ethyl acetate = 1:1) to obtain the title compound.

Yield: 1.552 g (6.25 mmol), 28 %

MS (ESI, m/z) 247 $(M-H)^-$

^{1}H-NMR ($CDCl_3$): 5.90 (1H, s), 6.94 (2H, q), 7.30-7.46 (8H, m).

Step 2

Synthesis of t-butyl 2-[(5H-dibenzo[a,d][7]annulen-5-ylidenacetyl)amino] -ethylcarbamate:

173 mg (0.70 mmol) of 5H-dibenzo[a,d][7]annulen-5-ylidenacetic acid, 124 mg (0.77 mmol) of t-butyl N-(2-aminoethyl)carbamate, 143 mg (0.75 mmol) of 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide hydrochloride and 0.11 ml (0.79 mmol) of triethylamine were stirred in 5 ml of dichloromethane at room temperature overnight. The reaction mixture was washed with saturated aqueous sodium hydrogencarbonate solution and the organic layer was dried over anhydrous sodium sulfate and then concentrated under reduced pressure. The residue was purified by the silica gel chromatography (hexane : ethyl acetate = 7:3) to obtain the title compound.

Yield: 185 mg (0.47 mmol), 68 %

MS (ESI, m/z) 391 $(M+H)^+$

^{1}H-NMR ($CDCl_3$): 1.44 (9H, s), 2.78-3.08 (3H, m), 3.27-3.42 (1H, m), 4.36 (1H, s), 5.31 (1H, s), 5.98 (1H, s), 6.49 (2H, s), 7.29-7.50 (8H, m).

Example 41

Synthesis of t-butyl 3-[(5H-dibenzo[a,d][7]annulen-5-ylidenacetyl)amino] -propylcarbamate:

173 mg (0.70 mmol) of 5H-dibenzo[a,d][7]annulen-5-ylidenacetic acid, 130 mg (0.75 mmol) of t-butyl N-(3-aminopropyl)carbamate, 149 mg (0.78 mmol) of 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide hydrochloride and 0.11 ml (0.79 mmol) of triethylamine were stirred in 5 ml of dichloromethane at room temperature overnight. The reaction mixture was washed with 0.5 N aqueous sodium hydroxide solution and the organic layer was dried over anhydrous sodium sulfate and then

concentrated under reduced pressure. The residue was purified by the silica gel chromatography (hexane : ethyl acetate = 7:3) to obtain the title compound.

Yield: 232 mg (0.57 mmol), 82 %

MS (ESI, m/z) 403 $(M-H)^-$

^{1}H-NMR ($CDCl_3$): 1.24-1.37 (2H, m), 1.42 (9H, s), 2.82 (2H, q), 2.90-3.04 (1H, m), 3.15-3.30 (1H, m), 4.77 (1H, s), 5.48 (1H, s), 5.98 (1H, s), 6.93 (2H, d), 7.29-7.50 (8H, m).

Example 42

Synthesis of t-butyl 4-(5H-dibenzo[a,d][7]annulen-5-ylidenacetyl)-1-piperazine carboxylate:

172 mg (0.69 mmol) of 5H-dibenzo[a,d][7]annulen-5-ylideneacetic acid, 144 mg (0.78 mmol) of t-butyl 1-piperazinecarboxylate, 148 mg (0.77 mmol) of 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide hydrochloride and 0.11 ml (0.79 mmol) of triethylamine were stirred in 5 ml of dichloromethane at room temperature overnight. The reaction mixture was washed with 0.5 N aqueous sodium hydroxide solution and the organic layer was dried over anhydrous sodium sulfate and then concentrated under reduced pressure. The residue was purified by the silica gel chromatography (hexane : ethyl acetate = 2:1) to obtain the title compound.

Yield: 273 mg (0.66 mmol), 95 %

MS (ESI, m/z) 417 $(M+H)^+$

^{1}H-NMR ($CDCl_3$): 1.42 (9H, s), 2.01-2.12 (1H, m), 2.71-2.84 (1H, m), 2.96-3.10 (2H, m), 3.11-3.26 (2H, m), 3.35-3.49 (1H, m), 3.55-3.69 (1H, m), 5.94 (1H, s), 6.83-6.96 (2H, m), 7.28-7.57 (8H, m).

Example 43

Synthesis of 1-ethyl-1-methylpropyl 2-[4-[(5H-dibenzo[a,d][7]annulen-5-ylidene)-1-piperidinyl]-2-oxoethylcarbamate:

Step 1

Synthesis of ethyl {[(1-ethyl-1-methylpropoxy)carbonyl]amino}acetate:

0.500 ml (4.01 mmol) of ethyl isocyanatoacetate was dissolved in dichloromethane. 0.05 ml of 4 N hydrochloric acid / 1,4-dioxane solution was added to the obtained solution, and they were stirred at room temperature for 5 minutes. 0.547 ml (4.41 mmol) of 3-methyl-3-pentanol was added to the reaction mixture, and they were stirred overnight. After the concentration under reduced pressure, ethyl acetate was added to the reaction mixture, and they were washed with saturated aqueous sodium hydrogencarbonate solution, dried over anhydrous sodium sulfate and then concentrated under reduced pressure. The residue was washed with diethyl ether. The filtrate was concentrated under reduced pressure to obtain the title compound.

Yield: 622 mg (2.69 mmol), 67 %

^{1}H-NMR ($CDCl_3$): 0.85 (6H, t), 1.26 (3H, t), 1.35 (3H, s), 1.66-1.91 (4H, m), 3.87 (2H, d), 4.19 (2H, q), 5.04 (1H, br s).

Step 2

Synthesis of {[(1-ethyl-1-methylpropoxy)carbonyl]amino}acetic acid:

300 mg (1.30 mmol) of ethyl {[(1-ethyl-1-methylpropoxy)carbonyl]-amino}acetate was dissolved in 2.5 ml of a solvent mixture of methanol : water (2.3 : 1). 1.56 ml of 1 N aqueous lithium hydroxide solution was added to the obtained solution. After stirring at room temperature for 2 hours, "DOWEX" (50W-X2 100 to 200 mesh H form) (an exchange resin of The Dow Chemical Company) was added to the reaction mixture under gentle stirring until pH of the mixture had become 5. The resin was

obtained by the filtration under suction and then the filtrate was concentrated under reduced pressure and then dried to obtain the title compound.

Yield: 284 mg (1.40 mmol), 100 %

MS (ESI, m/z) 202 $(M-H)^-$

^{1}H-NMR ($CDCl_3$): 0.82 (6H, br t), 1.33 (3H, s), 1.67-1.84 (4H, m), 3.69 (2H, br s), 5.86 (1H, br s).

Step 3

Synthesis of 1-ethyl-1-methylpropyl 2-[4-(5H-dibenzo[a,d][7]annulen-5-ylidene)-1-piperidinyl]-2-oxoethylcarbamate:

284 mg (1.40 mmol) of {[(1-ethyl-1-methylpropoxy)carbonyl]-amino}-acetic acid, 320 mg (1.17 mmol) of 4-(5H-dibenzo[a,d][7]annulen-5-ylidene)-piperidine and 322 mg (1.68 mmol) of 1-ethyl-3-(3'-dimethyl aminopropyl)carbodiimide hydrochloride were dissolved in a mixed solvent of 15 ml of dichloromethane and 5 ml of dimethylformamide. 0.23 ml (1.68 mmol) of triethylamine and 14.7 mg (0.12 mmol) of dimethylaminopyridine were added to the obtained solution, and they were stirred at room temperature overnight. After the concentration under reduced pressure, ethyl acetate was added to the reaction mixture. The resultant mixture was washed with saturated aqueous sodium chloride solution. The organic layer was dried over anhydrous magnesium sulfate and then concentrated under reduced pressure. The obtained residue was purified by the silica gel chromatography (hexane : dichloromethane = 95:5 to 2:3) to obtain the title compound.

Yield: 204 mg (0.445 mmol) (38 %)

MS (ESI, m/z) 459 $(M+H)^+$

^{1}H-NMR ($CDCl_3$): 0.85 (6H, t), 1.35 (3H, s), 1.66-1.91 (4H, m), 2.14-2.33

(4H, m), 2.97-3.06 (2H, m), 3.39-3.46 (1H, m), 3.84-4.00 (3H, m), 5.54 (1H, br s), 6.92 (2H, s), 7.15-7.18 (2H, m), 7.23-7.28 (2H, m), 7.31-7.37 (4H, m).

Example 44

Synthesis of N-(t-butyl)-4-[4-(10,11-dihydro-5H-dibenzo[b,f]azepin-5-yl) -1-piperidinyl]-4-oxobutanamide:

Step 1

Synthesis of 4-(t-butylamino)-4-oxobutanoic acid:

3.07 g (30.6 mmol) of succinic anhydride was suspended in 30 ml of dichloromethane. 4.1 ml (34.5 mmol) of t-butylamine was dropped into the suspension, and the resultant mixture was stirred at room temperature for 1 hour. White crystals thus formed were washed with ethyl acetate and then dissolved in 40 ml of 1 N aqueous sodium hydroxide solution. The resultant solution was stirred at room temperature for 2 hours and then acidified with 1 N aqueous hydrochloric acid solution under cooling with ice. After extracting with ethyl acetate, the organic layer was dried over anhydrous sodium sulfate and then concentrated under reduced pressure to obtain the title compound.

Yield: 2.75 g (15.9 mmol), 52 %

MS (ESI, m/z) 172 $(M-H)^-$

^{1}H-NMR (DMSO-d_6): 1.20 (9H, s), 2.21-2.26 (2H, m), 2.32-2.37 (2H, m), 7.39 (1H, br s).

Step 2

Synthesis of N-(t-butyl)-4-[4-(10,11-dihydro-5H-dibenzo[b,f]azepin-5-yl) -1-piperidinyl]-4-oxobutanamide:

83.2 mg (0.299 mmol) of 5-(4-piperidinyl)-10,11-dihydro-5H-

dibenzo[b,f]azepine, 62.2 mg (0.359 mmol) of 4-(t-butylamino)-4-oxobutanoic acid and 82.6 mg (0.431 mmol) of 1-ethyl-3-(3'-dimethyl aminopropyl)carbodiimide hydrochloride were dissolved in 5 ml of dichloromethane. 0.06 ml (0.431 mmol) of triethylamine and 3.67 mg (0.03 mmol) of 4-dimethylaminopyridine were added to the obtained solution, and they were stirred at room temperature overnight. The reaction mixture was concentrated under reduced pressure. Ethyl acetate was added thereto. After washing with 1 N aqueous hydrochloric acid solution, the organic layer was dried over anhydrous magnesium sulfate and then concentrated under reduced pressure. The residue was purified by the silica gel chromatography (dichloromethane : methanol = 9:1) to obtain the title compound.

Yield: 102 mg (0.236 mmol), 79 %

MS (ESI, m/z) 434 $(M+H)^+$

^{1}H-NMR ($CDCl_3$): 1.31 (9H, s), 1.58-1.70 (2H, m), 1.96-2.11 (2H, m), 2.37-2.42 (2H, m), 2.50-2.82 (4H, m), 3.14-3.26 (2H, m), 3.49 (2H, br s), 3.62-3.69 (1H, m), 3.92-4.00 (1H, m), 4.14-4.21 (1H, m), 5.78 (1H, br s), 6.92-6.99 (2H, m), 7.08-7.10 (6H, m).

Example 45

Synthesis of N-{2-[4-(5H-dibenzo[a,d][7]annulen-5-ylidene)-1-piperidinyl] -2-oxoethyl}-N,N-dimethylurea:

200 mg (0.545 mmol) of 2-[4-(5H-dibenzo[a,d][7]annulen-5-ylidene)-1-piperidinyl]-2-oxoethanamine dihydrochloride was suspended in 2 ml of dichloromethane. 0.19 ml of triethylamine was added to the obtained suspension. A solution of 70.3 mg (0.654 mmol) of N,N-dimethylcarbamoyl chloride in 3 ml of dichloromethane was added dropwise to the resultant mixture under cooling with ice, and they were

stirred at room temperature for 30 minutes. Dichloromethane was concentrated under reduced pressure. Ethyl acetate was added to the residue. The resultant mixture was washed with saturated aqueous sodium hydrogencarbonate solution. White crystals precipitated in the organic layer was taken by the filtration to obtain the title compound.

Yield: 158 mg (0.394 mmol), 72 %

MS (ESI, m/z) 430 $(M+H)^+$

^{1}H-NMR ($CDCl_3$): 2.20-2.33 (4H, m), 2.93 (6H, s), 3.01-3.10 (2H, m), 3.44-3.54 (1H, m), 3.92-4.05 (3H, m), 5.51 (1H, br s), 6.92 (2H, s), 7.15-7.19 (2H, m), 7.23-7.28 (2H, m), 7.32-7.36 (4H, m).

Example 46

Synthesis of N-{2-[4-(5H-dibenzo[a,d][7]annulen-5-ylidene)-1-piperidinyl]-2-oxoethyl}-1-piperidinecarboxamide:

200 mg (0.545 mmol) of 2-[4-(5H-dibenzo[a,d][7]annulen-5-ylidene)-1-piperidinyl]-2-oxoethanamine dihydrochloride was suspended in 2 ml of dichloromethane. 0.19 ml of triethylamine was added to the obtained suspension. A solution of 96.5 mg (0.654 mmol) of 1-piperidinecarbonyl chloride in 3 ml of dichloromethane was added dropwise to the resultant mixture under cooling with ice, and they were stirred at room temperature for 30 minutes. Dichloromethane was concentrated under reduced pressure. Ethyl acetate was added to the residue. The resultant mixture was washed with saturated aqueous sodium hydrogencarbonate solution. The organic layer was dried over anhydrous magnesium sulfate and then concentrated under reduced pressure. The residue was purified by the basic silica gel chromatography (hexane : ethyl acetate = 4:1 to 1:4) to obtain the title compound.

Yield: 201 mg (0.455 mmol), 84 %

MS (ESI, m/z) 442 $(M+H)^+$

^{1}H-NMR ($CDCl_3$): 1.49-1.62 (6H, m), 2.15-2.33 (4H, m), 3.02-3.08 (2H, m), 3.34-3.37 (4H, m), 3.45-3.51 (1H, m), 3.90-4.11 (3H, m), 5.58 (1H, br s), 6.92 (2H, s), 7.16-7.18 (2H, m), 7.28-7.35 (6H, m).

Example 47

Synthesis of N-[2-(t-butylamino)-2-oxoethyl]-4-(5H-dibenzo[a,d][7]annulen-5-ylidene)-1-piperidinecarboxamide:

Step 1

Synthesis of t-butyl ({[4-(5H-dibenzo[a,d][7]annulen-5-ylidene)-1-piperidinyl]-carbonyl}amino)acetate:

475 mg (2.93 mmol) of N,N'-carbonyldiimidazole was dissolved in 10 ml of anhydrous tetrahydrofuran. 0.45 ml (3.29 mmol) of triethylamine was added to the obtained solution, and they were stirred at room temperature for 10 minutes. The reaction mixture was cooled with ice, and 460 mg (2.74 mmol) of t-butyl aminoacetate hydrochloride was added dropwise to the mixture during a period of about 10 minutes, and they were stirred at room temperature for 1 hour. After cooling with ice, 500 mg (1.83 mmol) of 4-(5H-dibenzo[a,d][7]annulen-5-ylidene) piperidine was added to the resultant mixture, and they were stirred at room temperature overnight. Water was added to the reaction mixture. After extracting with ethyl acetate followed by drying over anhydrous magnesium sulfate, the product was concentrated under reduced pressure. The residue thus obtained was purified by the silica gel chromatography (dichloromethane : methanol = 95:5 to 2:3) to obtain the title compound.

Yield: 752 mg (1.75 mmol), 95 %

MS (ESI, m/z) 431 $(M+H)^+$

^{1}H-NMR ($CDCl_3$): 1.46 (9H, s), 2.12-2.20 (2H, m), 2.28-2.33 (2H, m), 3.01-3.09 (2H, m), 3.52-3.59 (2H, m), 3.90 (2H, d), 4.91 (1H, br t).

Step 2

Synthesis of ({[4-(5H-dibenzo[a,d][7]annulen-5-ylidene)-1-piperidinyl]-carbonyl}amino)acetic acid:

752 mg (1.75 mmol) of t-butyl ({[4-(5H-dibenzo[a,d][7]annulen-5-ylidene)-1-pipieidinyl]carbonyl}amino)acetate was dissolved in 8 ml of dichloromethane. 2 ml of trifluoroacetic acid was added to the obtained solution under cooling with ice, and they were stirred at room temperature for 1 hour. After the concentration under reduced pressure, the reaction mixture was dissolved in ethyl acetate. Water was added thereto and white crystals thus precipitated were taken by the filtration to obtain the title compound.

Yield: 498 mg (1.33 mmol), 76 %

MS (ESI, m/z) 373 $(M-H)^-$

^{1}H-NMR (DMSO-d_6): 1.85-1.93 (2H, m), 2.16-2.25 (2H, m), 3.03-3.11 (2H, m), 3.39-3.47 (2H, m), 3.62 (2H, d), 6.82 (1H, br t), 6.96 (2H, s), 7.19-7.30 (4H, m), 7.35-7.40 (4H, m), 12.28 (1H, br s).

Step 3

Synthesis of N-[2-(t-butylamino)-2-oxoethyl]-4-(5H-dibenzo[a,d][7]annulen-5-ylidene)-1-piperidinecarboxamide:

300 mg (0.801 mmol) of ({[4-(5H-dibenzo[a,d][7]annulen-5-ylidene)-1-piperidinyl] carbonyl} amino)acetic acid, 1.0 ml (0.961 mmol) of t-butylamine and 230 mg (1.20 mmol) of 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide hydrochloride were dissolved in 10 ml of dichloromethane. The obtained solution was

stirred at room temperature for 1 hour. Water was added to the reaction mixture. After extracting with dichloromethane, the dichloromethane layer was dried over anhydrous magnesium sulfate and then concentrated under reduced pressure. The residue thus obtained was purified by the silica gel chromatography (dichloromethane : methanol = 4:1 to 1:9) to obtain the title compound.

Yield: 198 mg (0.476 mmol), 60 %

MS (ESI, m/z) 430 $(M+H)^+$

^{1}H-NMR ($CDCl_3$): 1.34 (9H, s), 2.11-2.18 (2H, m), 2.27-2.36 (2H, m), 3.00-3.09 (2H, m), 3.52-.3.59 (2H, m), 3.79 (2H, d), 5.28 (1H, br s), 6.01 (1H, br s), 6.91 (2H, s), 7.15-7.18 (2H, m), 7.22-7.27 (2H, m), 7.30-7.35 (4H, m).

Example 48

Synthesis of N-[2-[4-(5H-dibenzo[a,d][7]annulen-5-ylidene)-1-piperidinyl]-1-(hydroxymethyl)-2-oxoethyl]-1-piperidinecarboxamide:

Step 1

Synthesis of methyl 3-hydroxy-2-[(1-piperidinylcarbonyl)amino] propionate:

1.00 g (6.43 mmol) of methyl 2-amino-3-hydroxypropionate hydrochloride and 960 mg (14.1 mmol) of imidazole were dissolved in 10 ml of dichloromethane. 10 ml of a solution of 1.07 g (7.07 mmol) of t-butyldimethylchlorosilane in dichloromethane was added dropwise to the obtained solution under cooling with ice, and they were stirred at room temperature for 1 hour. After concentrating under reduced pressure, ethyl acetate was added to the residue. The reaction mixture was washed with saturated aqueous ammonium chloride solution, then dried over anhydrous magnesium sulfate and concentrated under

reduced pressure. The residue was dissolved in 10 ml of dichloromethane. 1.35 ml (9.65 mmol) of triethylamine and 0.97 ml (7.72 mmol) of 1-piperidinecarbonyl chloride were added dropwise to the obtained solution under cooling with ice, and they were stirred at room temperature overnight. 20 ml of chloroform was added to the reaction mixture, and they were stirred at 50°C for 3 hours and then concentrated under reduced pressure. The residue was dissolved in 15 ml of methanol. 10 ml of 2 N hydrochloric acid was added dropwise to the obtained solution under cooling with ice, and they were stirred at room temperature for 2 hours. After the concentration under reduced pressure, ethyl acetate was added to the residue. The product was washed with 1 N aqueous hydrochloric acid solution, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue thus obtained was purified by the silica gel chromatography (dichloromethane : methanol = 1:0 to 9:1) to obtain the title compound.

Yield: 428 mg (1.86 mmol), 29 %

MS (ESI, m/z) 231 $(M+H)^+$

^{1}H-NMR ($CDCl_3$): 1.57-1.59 (6H, m), 2.98 (1H, br s), 3.36-3.39 (4H, m), 3.79 (3H, s), 3.87-3.99 (2H, m), 4.58-4.63 (1H, m), 5.43 (1H, br d).

Step 2

Synthesis of 3-hydroxy-2-[(1-piperidinylcarbonyl)amino]propionic acid:

200 mg (0.869 mmol) of methyl 3-hydroxy-2-[(1-piperidinyl carbonyl)-amino]propionate was dissolved in 6 ml of a solvent mixture of methanol : tetrahydrofuran (1:1). 1.04 ml (1.04 mmol) of 1 N aqueous lithium hydroxide solution was added to the obtained solution, and they were stirred at room temperature for 30 minutes. The reaction mixture was concentrated under reduced pressure, and the concentrate was

acidified with 1 N aqueous hydrochloric acid solution. After extracting with ethyl acetate, the organic layer was dried over anhydrous magnesium sulfate and then concentrated under reduced pressure to obtain the title compound.

Yield: 64 mg (0.296 mmol) (34 %)

MS (ESI, m/z) 215 $(M-H)^-$

^{1}H-NMR (CD_3OD): 1.51-1.69 (6H, m), 3.17-3.20 (1H, m), 3.38-3.42 (4H, m), 3.80-3.94 (2H, m), 4.36 (1H, t).

Step 3

Synthesis of N-[2-[4-(5H-dibenzo[a,d][7]annulen-5-ylidene)-1-piperidinyl]-1-(hydroxymethyl)-2-oxoethyl]-1-piperidinecarboxamide:

64.0 mg (0.296 mmol) of 3-hydroxy-2-[(1-piperidinylcarbonyl) amino]propionic acid, 80.9 mg (0.296 mmol) of 4-(5H-dibenzo[a,d][7] annulen-5-ylidene)piperidine and 85.1 mg (0.444 mmol) of 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide hydrochloride were dissolved in 10 ml of dichloromethane. 0.091 ml (0.651 mmol) of triethylamine was added to the obtained solution, and they were stirred at room temperature overnight. The reaction mixture was concentrated under reduced pressure. Ethyl acetate was added to the residue. After washing with saturated aqueous sodium chloride solution, the reaction product was dried over anhydrous magnesium sulfate and then concentrated under reduced pressure. The resultant product was purified by the silica gel chromatography (dichloromethane : methanol = 9:1) to obtain the title compound.

Yield: 100 mg (0.213 mmol) (72 %)

MS (ESI, m/z) 472 $(M+H)^+$

^{1}H-NMR ($CDCl_3$): 1.49-1.62 (6H, m), 2.26-2.35 (4H, m), 2.92-3.37 (6H,

m), 3.65-3.76 (3H, m), 3.83-4.01 (1H, m), 4.08-4.31 (1H, m), 4.76-4.82 (1H, m), 5.87-5.92 (1H, m), 6.92 (2H, d), 7.14-7.18 (2H, m), 7.23-7.28 (2H, m), 7.32-7.37 (4H, m).

Example 49

Synthesis of N-[2-(t-butylamino)-1-(hydroxymethyl)-2-oxoethyl]-4-(5H-dibenzo[a,d][7]annulen-5-ylidene)-1-piperidinecarboxamide:

Step 1

Synthesis of 2-{[(benzyloxy)carbonyl]amino}-3-{[t-butyl(dimethyl)silyl]oxy}-propionic acid:

1.50 g (6.27 mmol) of N-[(benzyloxy)carbonyl]-(DL)-serine was dissolved in 10 ml of N,N-dimethylformamide. 885 mg (13.2 mmol) of imidazole and 1.98 g (13.2 mmol) of t-butyldimethylchlorosilane were added to the obtained solution at 0°C, and they were stirred overnight. Water was added to the reaction mixture and they were stirred for 10 minutes. After extracting with ethyl acetate 3 times followed by the drying over anhydrous sodium sulfate, the solvent was evaporated under reduced pressure to obtain the title compound.

Yield: 2.21 g (6.27 mmol), 100 %

^{1}H-NMR ($CDCl_3$): -0.01-0.10 (6H, m), 0.62-0.94 (9H, m), 3.60-3.80 (1H, m), 4.05-4.15 (1H, m), 4.32-4.48 (1H, m), 5.05-5.20 (2H, m), 5.59 (1H, s), 7.28-7.40 (5H, m).

Step 2

Synthesis of 2-{[(benzyloxy)carbonyl]amino}-N-(t-butyl)-3-{[t-butyl(dimethyl)-silyl]oxy}propylamide:

2.21 g (6.27 mmol) of 2-{[(benzyloxy)carbonyl]amino}-3-{[t-butyl(dimethyl)silyl]oxy}propionic acid, 1.44 g (7.52 mmol) of 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide hydrochloride, 79.0 mg (0.63 mmol)

of 4-dimethylaminopyridine and 952 mg (9.41 mmol) of triethylamine were dissolved in 10 ml of dichloromethane. 504 mg (6.90 mmol) of t-butylamine was added to the obtained solution, and they were stirred overnight. Saturated aqueous ammonium chloride solution was added to the reaction mixture. After extracting with ethyl acetate 3 times followed by the drying over anhydrous sodium sulfate, the solvent was evaporated under reduced pressure. The residue was purified by the silica gel chromatography (hexane : ethyl acetate = 97:3 to 88:12) to obtain the title compound.

Yield: 1.07 g (2.62 mmol), 42 %

^{1}H-NMR ($CDCl_3$): 0.10 (6H, m), 0.90 (9H, s), 1.33 (9H, s), 3.56 (1H, t), 3.94-4.09 (2H, m), 5.12 (2H, m), 5.67 (1H, s), 6.30 (1H, s), 7.28-7.39 (5H, m).

Step 3

Synthesis of 2-amino-N-(t-butyl)-3-{[t-butyl(dimethyl)silyl]oxy}propylamide:

500 mg of palladium carbon (10 % w/v) in 5 ml of ethanol was added to 990 mg (2.42 mmol) of 2-{[(benzyloxy)carbonyl]amino}-N-(t-butyl)-3-{[t-butyl-(dimethyl)silyl]oxy}propylamide, and they were stirred in hydrogen gas atmosphere overnight. The reaction mixture was filtered, and the solvent was evaporated under reduced pressure to obtain the title compound. After drying on anhydrous sodium sulfate, the solvent was evaporated under reduced pressure to obtain the title compound.

Yield: 620 mg (2.26 mmol), 93 %

^{1}H-NMR ($CDCl_3$): 0.06 (6H, s), 0.89 (9H, s), 1.24 (9H, s), 1.63 (2H, s), 3.30 (1H, t), 3.76 (2H, d), 7.10 (1H, br s).

Step 4

Synthesis of N-[2-(t-butylamino)-1-({[t-butyl(dimethyl)silyl]oxy}methyl)-2-oxoethyl]-4-(5H-dibenzo[a,d][7]annulen-5-ylidene)-1-piperidinecarboxamide:

59.1 mg (0.364 mmol) of 1,1'-carbonylbis-1H-imidazole and 36.9 mg (0.364 mmol) of triethylamine were dissolved in 4 ml of dichloromethane. A solution of 100 mg (0.364 mmol) of 2-amino-N-(t-butyl)-3-{[t-butyl(dimethyl)-silyl]oxy}propylamide in 2 ml of dichloromethane was slowly added to the obtained solution. After stirring for 2 hours, a solution of 99.6 mg (0.364 mmol) of 2-[4-(5H-dibenzo[a,d][7]annulen-5-ylidene)-1-piperidinyl] ethylamine and 36.9 mg (0.364 mmol) of triethylamine in 2 ml of dichloromethane was slowly added to the reaction mixture. After stirring them overnight, the solvent was evaporated under reduced pressure and the residue was purified by the silica gel chromatography (hexane : ethyl acetate = 9:1 to 7:3) to obtain the title compound.

Yield: 113 mg (0.197 mmol), 54 %

^{1}H-NMR ($CDCl_3$): 0.11 (6H, d), 0.90 (9H, s), 1.24 (9H, s), 2.10-2.20 (2H, m), 2.25-2.40 (2H, m), 3.30-3.12 (2H, m), 3.46 (1H, t), 3.50-3.61 (2H, m), 3.97 (1H, dd), 4.10-4.18 (1H, m), 5.57 (1H, d), 6.60 (1H, s), 6.91 (2H, s), 7.13-7.36 (8H, m).

Step 5

Synthesis of N-[2-(t-butylamino)-1-(hydroxymethyl)-2-oxoethyl]-4-(5H-dibenzo[a,d][7]annulen-5-ylidene)-1-piperidinecarboxamide:

113 mg (0.197 mmol) of N-[2-(t-butylamino)-1-({[t-butyl(dimethyl)-silyl]oxy}methyl)-2-oxoethyl]-4-(5H-dibenzo[a,d][7]annulen-5-ylidene)-1-piperidinecarboxamide was dissolved in 3 ml of tetrahydrofuran. 0.22

ml of 1 M tetrabutylammonium fluoride / tetrahydrofuran solution was added to the obtained solution, and they were stirred for 30 minutes. After the purification by the silica gel chromatography (hexane : ethyl acetate = 9:1 to 3:2), the title compound was obtained.

Yield: 66.9 mg (0.146 mmol), 74 %

MS (ESI, m/z) 460$(M+H)^+$

^{1}H-NMR ($CDCl_3$): 1.35 (9H, s), 2.13-2.26 (2H, m), 2.28-2.42 (2H, m), 3.01-3.15 (2H, m), 3.50-3.64 (3H, m), 4.03-4.26 (2H, m), 5.64 (1H, d), 6.77 (1H, br s), 6.94 (2H, s), 7.16-7.40 (8H, m).

Example 50

Synthesis of methyl 2-[(t-butoxycarbonyl)amino]-4-[4-(5H-dibenzo[a,d][7]-annulen-5-ylidene)-1-piperidinyl]-4-oxobutanoate:

Step 1

Synthesis of 3-[(t-butoxycarbonyl)amino]-4-methoxy-4-oxobutanoic acid:

2.0 g (6.18 mmol) of 4-(benzyloxy)-2-[(t-butoxycarbonyl)amino]-4-oxobutanoic acid was dissolved in a solvent mixture of 6 ml of methanol and 12 ml of toluene. 3.7 ml of 2 M trimethylsilyldiazomethane / hexane solution was added to the obtained solution and they were stirred for 3 hours. Additional 0.5 ml of 2 M trimethylsilyldiazomethane / hexane solution was added to the reaction mixture and they were stirred for 1 hour. The solvent was evaporated under reduced pressure. The residue was dissolved in 20 ml of ethanol. 2.0 g of palladium carbon (10 % w/v) was added to the obtained solution, and they were stirred in hydrogen gas atmosphere for 19 hours. After the filtration, the solvent was evaporated under reduced pressure to obtain the title compound.

Yield: 1.50 g (6.07 mmol), 98 %

^{1}H-NMR (DMSO-d_6): 1.38 (9H, s), 2.49-2.70 (2H, m), 3.62 (3H, s), 4.32

(1H, m), 7.23 (1H, d).

Step 2

Synthesis of methyl 2-[(t-butoxycarbonyl)amino]-4-[4-(5H-dibenzo[a,d][7]-annulen-5-ylidene)-1-piperidinyl]-4-oxobutanoate:

1.10 g (4.04 mmol) of 4-(5H-dibenzo[a,d][7]annulen-5-ylidene)-1-piperidine, 1.00 g (4.04 mmol) of 3-[(t-butoxycarbonyl)amino]-4-methoxy-4-oxobutanoic acid, 930 mg (4.85 mmol) of 1-ethyl-3-(3'-dimethylamino propyl)-carbodiimide hydrochloride and 48.9 mg (0.40 mmol) of 4-dimethylaminopyridine were dissolved in 10 ml of dichloromethane. 532 mg (5.25 mmol) of triethylamine was added to the obtained solution, and they were stirred overnight. Saturated aqueous ammonium chloride solution was added to the reaction mixture. After extracting with ethyl acetate 3 times, the organic layer was washed with saturated sodium hydrogencarbonate solution and then dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified by the silica gel chromatography (hexane : ethyl acetate = 89:11) to obtain the title compound.

Yield: 1.17 g (2.32 mmol), 58 %

MS (ESI, m/z) 503 $(M+H)^+$

^{1}H-NMR ($CDCl_3$): 1.43 (9H, d), 2.10-2.38 (4H, m), 2.73 (1H, m), 2.90-3.18 (3H, m), 3.48-3.54 (1H, m), 3.73 (3H, d), 3.83-3.95 (1H, m), 4.49-4.58 (1H, m), 5.77 (1H, t), 6.91 (2H, s), 7.16-7.36 (8H, m).

Step 3

Synthesis of methyl 4-[4-(5H-dibenzo[a,d][7]annulen-5-ylidene)-1-piperidinyl]-2-[(2,2-dimethylpropanoyl)amino]-4-oxobutanoate:

600 mg (1.19 mmol) of methyl 2-[(t-butoxycarbonyl)amino]-4-[4-(5H-dibenzo[a,d][7]annulen-5-ylidene)-1-piperidinyl]-4-oxobutanoate was

dissolved in 5 ml of ethyl acetate. 0.5 ml of 4 N hydrochloric acid / ethyl acetate solution was added to the obtained solution, and they were stirred at 0°C for 3 hours. After stirring at room temperature overnight, the solvent was evaporated under reduced pressure. The residue was dissolved in 10 ml of dichloromethane. 602 mg (5.95 mmol) of triethylamine and 158 mg (1.31 mmol) of pivaloyl chloride were added to the obtained solution, and they were stirred for 10 minutes. Saturated aqueous sodium hydrogencarbonate solution and water were added to the reaction mixture. After extracting with ethyl acetate 3 times followed by the drying over anhydrous sodium sulfate, the solvent was evaporated under reduced pressure, and the residue was purified by the silica gel chromatography (hexane : ethyl acetate = 89:11 to 65:35) to obtain the title compound.

Yield: 468 mg (0.962 mmol), 81 %

MS (ESI, m/z) 487 $(M+H)^+$

^{1}H-NMR ($CDCl_3$): 1.20 (9H, d), 2.10-2.38 (4H, m), 2.60-2.81 (1H, m), 2.85-3.20 (3H, m), 3.42-3.57 (1H, m), 3.74 (3H, d), 3.80-3.98 (1H, m), 4.85 (1H, m), 6.92 (2H, s), 7.03 (1H, d), 7.11-7.38 (8H, m).

Step 4

Synthesis of N-[3-[4-(5H-dibenzo[a,d][7]annulen-5-ylidene)-1-piperidinyl]-1-(hydroxymethyl)-3-oxopropyl]-2,2-dimethylpropanamide:

106 mg (0.218 mmol) of methyl 4-[4-(5H-dibenzo[a,d][7]annulen-5-ylidene)-1-piperidinyl]-2-[(2,2-dimethylpropanoyl)amino]-4-oxobutanoate was dissolved in 3 ml of tetrahydrofuran. 5.7 mg (0.261 mmol) of lithium borohydride was added to the obtained solution at 0°C. The reaction mixture was stirred for 1.5 hours and then saturated aqueous ammonium chloride solution was added thereto. After extracting with

ethyl acetate 3 times, the extract was dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure to obtain the title compound.

Yield: 72.3 mg (0.158 mmol), 72 %

MS (ESI, m/z) 459 $(M+H)^+$

^{1}H-NMR ($CDCl_3$): 1.18 (9H, d), 2.11-2.35 (4H, m), 2.58-2.71 (2H, m), 2.88-3.21 (2H, m), 3.56-3.79 (3H, m), 3.85-4.15 (3H, m), 6.95-7.00 (3H, m), 7.11-7.33 (8H, m).

Example 51

Synthesis of cyclohexyl 2-[4-(5H-dibenzo[a,d][7]annulen-5-ylidene)-1-piperidinyl]-2-oxoethylcarbamate:

Step 1

Synthesis of {[(cyclohexyloxy)carbonyl]amino}acetic acid:

620 mg (4.80 mmol) of ethyl isocyanatoacetate was dissolved in 5 ml of dichloromethane. 10 ml of a solution of 0.56 ml (5.28 mmol) of cyclohexanol in 10 ml of dichloromethane was added to the obtained solution under cooling with ice, and they were stirred at room temperature for 15 minutes. The reaction mixture was concentrated under reduced pressure. 5.8 ml of 1 N aqueous lithium hydroxide solution was added to the concentrate, and the obtained mixture was stirred in a solvent mixture of methanol : water = 2:1 at room temperature for 2 hours. The reaction mixture was concentrated under reduced pressure. Water was added to the concentrate and the resultant aqueous layer was washed with ethyl acetate. 0.1 N aqueous hydrochloric acid solution was added to the aqueous layer to control pH at 2 to 3. After extracting with ethyl acetate, the organic layer was dried over anhydrous magnesium sulfate and then concentrated under

reduced pressure to obtain the title compound.

Yield: 86.1 mg (0.428 mmol), 8.9 %

MS (ESI, m/z) 200 $(M-H)^-$

^{1}H-NMR ($CDCl_3$): 1.22-1.56 (6H, m), 1.65-1.76 (2H, m), 1.80-1.92 (2H, m), 3.95-4.02 (2H, m), 4.65 (1H, br s), 5.15 (1H, br s).

Step 2

Synthesis of cyclohexyl 2-[4-(5H-dibenzo[a,d][7]annulen-5-ylidene)-1-piperidinyl]-2-oxoethylcarbamate:

86.1 mg (0.428 mmol) of {[(cyclohexyloxy)carbonyl]amino}acetic acid, 176 mg (0.642 mmol) of 4-(5H-dibenzo[a,d][7]annulen-5-ylidene) piperidine and 98.5 mg (0.514 mmol) of 1-ethyl-3-(3'-dimethylamino propyl)carbodiimide hydrochloride were suspended in 10 ml of dichloromethane. 0.086 ml (0.617 mmol) of triethylamine was added to the obtained suspension, and they were stirred at room temperature for 3 hours. The resultant mixture was concentrated under reduced pressure and then ethyl acetate was added to the residue. The resultant mixture was washed with saturated aqueous sodium hydrogencarbonate solution, dried over anhydrous magnesium sulfate and then concentrated under reduced pressure. The obtained residue was purified by the silica gel chromatography (hexane : ethyl acetate = 95:5 to 1:4) to obtain the title compound.

Yield: 82.9 mg (0.182 mmol), 43 %

MS (ESI, m/z) 457 $(M+H)^+$

^{1}H-NMR ($CDCl_3$): 1.32-1.42 (4H, m), 1.45-1.57 (3H, m), 1.64-1.75 (2H, m), 1.80-1.90 (2H, m), 2.15-2.34 (4H, m), 2.99-3.08 (2H, m), 3.41-3.47 (1H, m), 3.88-3.99 (2H, m), 4.58-4.67 (1H, m), 5.62 (1H, br s), 6.92 (2H, s), 7.15-7.18 (2H, m), 7.23-7.24 (1H, m), 7.28-7.29 (1H, m), 7.32-7.37 (4H,

m).

Example 52

Synthesis of 1-methylcyclopentyl 2-[4-(5H-dibenzo[a,d][7]annulen-5-ylidene)-1-piperidinyl]-2-oxoethylcarbamate:

Step 1

Synthesis of ({[(1-methylcyclopentyl)oxy]carbonyl}amino)acetic acid:

500 mg (3.87 mmol) of ethyl isocyanatoacetate was dissolved in 5 ml of dichloromethane. 0.05 ml of 4 N hydrochloric acid / 1,4-dioxane solution was added to the obtained solution. 465 mg (4.64 mmol) of 1-methylcyclopentanol was added to the resultant mixture, and they were stirred for 3 hours 30 minutes. 10 ml of methanol and 12 ml of 1 N aqueous sodium hydroxide solution were added thereto and they were stirred for 15 minutes. The organic solvent was evaporated under reduced pressure. After extracting with dichloromethane twice, the aqueous layer was neutralized with 1 N aqueous hydrochloric acid solution. The product was extracted with dichloromethane 3 times and then dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure to obtain the title compound. The product was subjected to the next reaction without any purification.

Yield: 43.0 mg (0.214 mmol), 5.5 %

^{1}H-NMR ($CDCl_3$): (Only the main peaks are shown because the product contained impurities) 1.56 (3H, s), 5.22 (1H, d).

Step 2

Synthesis of 1-methylcyclopentyl 2-[4-(5H-dibenzo[a,d][7]annulen-5-ylidene)-1-piperidinyl]-2-oxoethylcarbamate:

70.2 mg (0.257 mmol) of 4-(5H-dibenzo[a,d][7]annulen-5-ylidene)-1-piperidine, 43.0 mg (0.214 mmol) of ({[(1-methylcyclopentyl)oxy] carbonyl}amino)acetic acid, 49.3 mg (0.257 mmol) of 1-ethyl-3-

(3'-dimethylaminopropyl)carbodiimide hydrochloride and 3.6 mg (0.03 mmol) of 4-dimethylaminopyridine were dissolved in 1 ml of dichloromethane. 26.0 mg (0.257 mmol) of triethylamine was added to the obtained solution, and they were stirred overnight. After the purification by the silica gel chromatography (hexane : ethyl acetate = 9:1 to 3:2), the title compound was obtained.

Yield: 56.7 mg (0.124 mmol), 58 %

MS (ESI, m/z) 457 $(M+H)^+$

^{1}H-NMR ($CDCl_3$): 1.48-1.76 (9H, m), 2.00-2.36 (6H, m), 3.02 (2H, m), 3.37-3.50 (1H, m), 3.80-4.05 (3H, m), 5.53 (1H, s), 6.92 (2H, s), 7.13-7.20 (2H, m), 7.22-7.37 (6H, m).

Example 53

Synthesis of tetrahydro-2H-pyran-4-yl 2-[4-(5H-dibenzo[a,d][7]annulen-5-ylidene)-1-piperidinyl]-2-oxoethylcarbamate:

Step 1

Synthesis of ethyl {[(tetrahydro-2H-pyran-4-yloxy)carbonyl]amino} acetate:

0.600 ml (4.80 mmol) of ethyl isocyanatoacetate was dissolved in dichloromethane. 0.06 ml of 4 N hydrochloric acid / 1,4-dioxane solution was added to the obtained solution, and they were stirred at room temperature for 5 minutes. 0.503 ml (5.28 mmol) of tetrahydro-4H-4-pyranol was added to the reaction mixture, and they were stirred at room temperature overnight. After concentrating the reaction mixture under reduced pressure, the residue was purified by the silica gel chromatography (hexane : ethyl acetate = 9:1 to 1:4), the title compound was obtained.

Yield: 584 mg (2.53 mmol), 53 %

^{1}H-NMR ($CDCl_3$): 1.29 (3H, t), 1.61-1.73 (2H, m), 1.89-1.97 (2H, m), 3.49-3.56 (2H, m), 3.87-3.96 (4H, m), 4.22 (2H, q), 4.81-4.90 (1H, m), 5.13-5.20 (1H, br s).

Step 2

Synthesis of {[(tetrahydro-2H-pyran-4-yloxy)carbonyl]amino}acetic acid:

The title compound was obtained from 287 mg (1.24 mmol) of ethyl {[(tetrahydro-2H-pyran-4-yloxy)carbonyl]amino}acetate and 1.49 ml of 1 N aqueous lithium hydroxide solution in the same manner as that in Step 2 in Example 43.

Yield: 269 mg (1.32 mmol), 100 %

MS (ESI, m/z) 202 $(M-H)^-$

^{1}H-NMR (DMSO-d_6): 1.40-1.52 (2H, m), 1.77-1.83 (2H, m), 3.28-3.43 (4H, m), 3.73-3.80 (2H, m), 4.63 (1H, sept), 6.31 (1H, br s).

Step 3

Synthesis of tetrahydro-2H-pyran-4-yl 2-[4-(5H-dibenzo[a,d][7]annulen-5-ylidene)-1-piperidinyl]-2-oxoethylcarbamate:

Tetrahydro-2H-pyran-4-yloxy)carbonyl]amino}acetic acid, 563 mg (2.06 mmol) of 4-(5H-dibenzo[a,d][7]annulen-5-ylidene) piperide and 563 mg (1.65 mmol) of 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide hydrochloride were suspended in 10 ml of dichloromethane. 0.23 ml (1.65 mmol) of triethylamine was added to the obtained suspension, and they were stirred at room temperature overnight. 20 ml of dimethylformamide was added to the reaction mixture, and they were stirred at 50°C for 3 hours. 263 mg (1.37 mmol) of 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide hydrochloride, 50 mg (0.41 mmol) of 4-dimethylaminopyridine and 0.19 ml (1.37 mmol) of triethylamine were added to the reaction mixture, and they were stirred

at 50°C overnight. The resultant mixture was concentrated under reduced pressure and then ethyl acetate was added to the residue. The resultant mixture was washed with saturated aqueous sodium hydrogencarbonate solution and saturated aqueous sodium chloride solution. The organic layer was dried over anhydrous magnesium sulfate and then concentrated under reduced pressure. The obtained residue was purified by the silica gel chromatography (hexane : ethyl acetate = 3:1 to 1:2) to obtain the title compound.

Yield: 32.1 mg (0.0700 mmol), 5.1 %

MS (ESI, m/z) 459 $(M+H)^+$

^{1}H-NMR ($CDCl_3$): 1.62-1.72 (2H, m), 1.87-1.96 (2H, m), 2.15-2.33 (4H, m), 2.99-3.08 (2H, m), 3.42-3.56 (3H, m), 3.86-4.13 (5 H, m), 4.81-4.86 (1H, m), 5.70 (1H, br t), 6.92 (2H, s), 7.15-7.18 (2H, m), 7.23-7.29 (2H, m), 7.32-7.37 (4H, m).

The structural formulae of the compounds obtained in Examples 1 to 53 are shown in Tables 1 to7.

Table 1

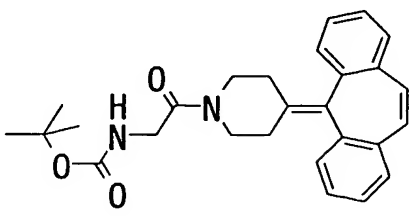
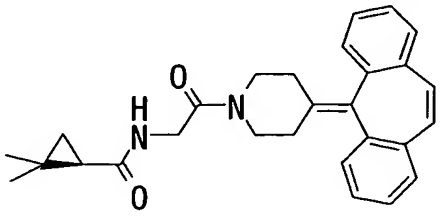
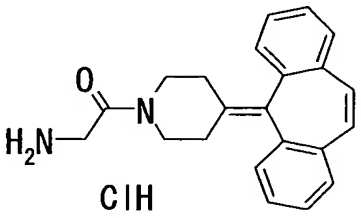
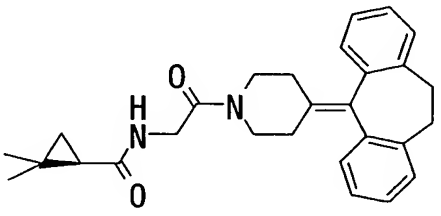
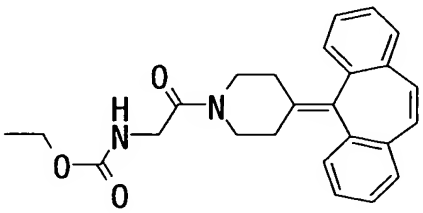
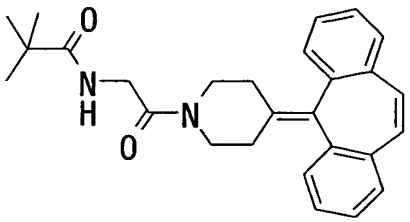
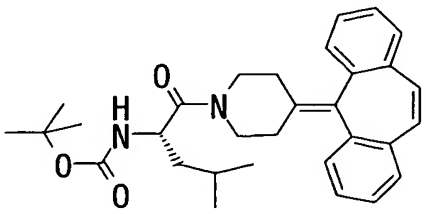
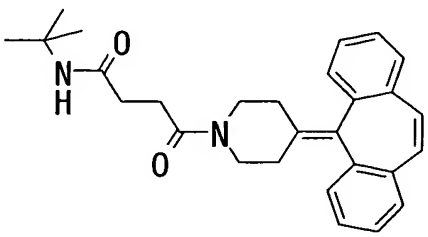
Ex.	Structural formula	Ex.	Structural formula
1		5	chiral 
2		6	chiral 
3		8	
4	chiral 	9	

Table 2

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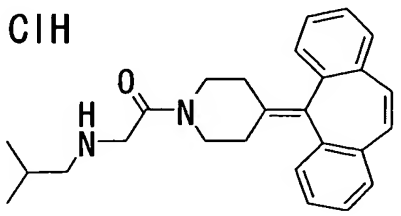
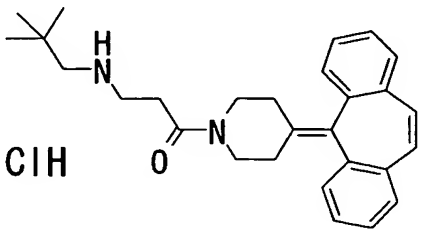
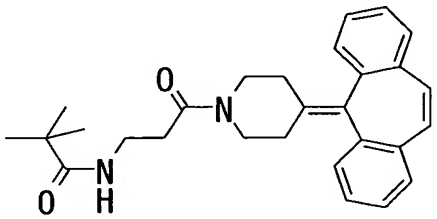
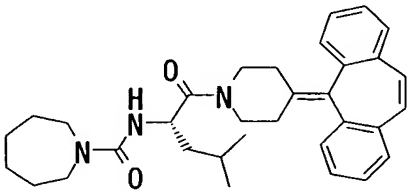
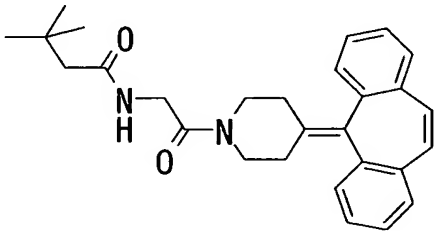
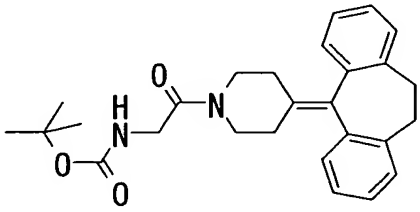
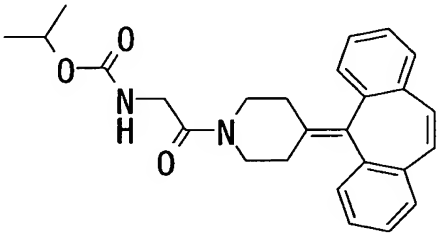
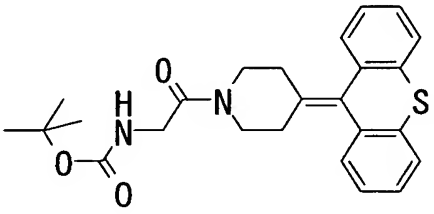
10		14	
11		15	chiral 
12		16	
13		17	

Table 3

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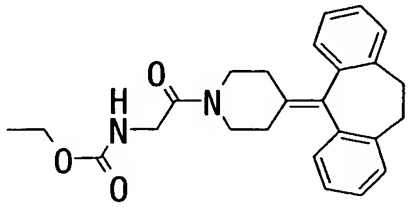
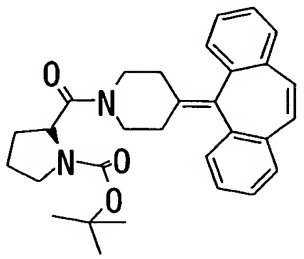
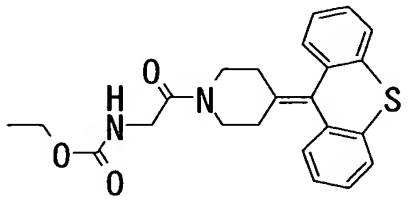
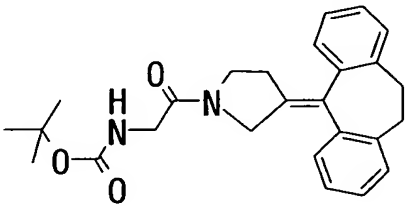
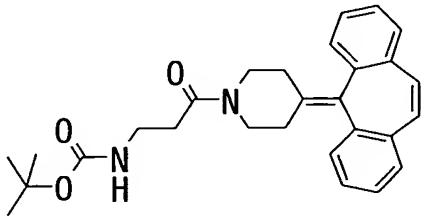
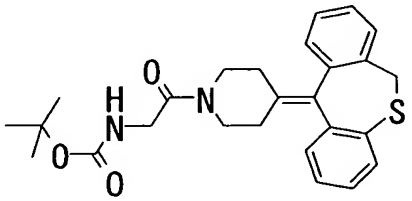
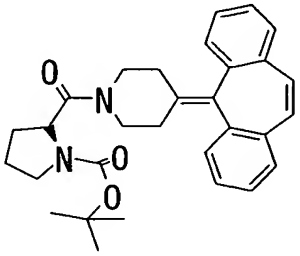
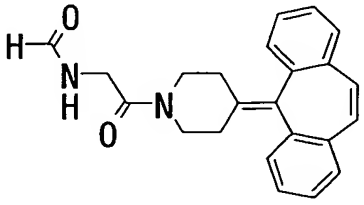
18		22	chiral 
19		23	
20		24	
21	chiral 	25	

Table 4

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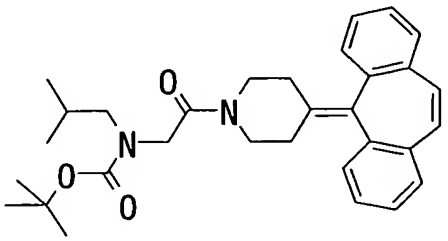
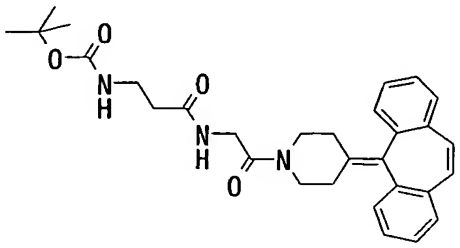
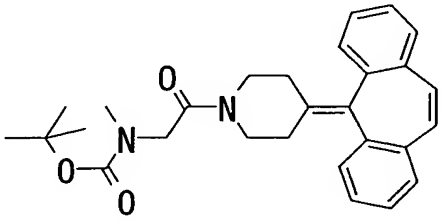
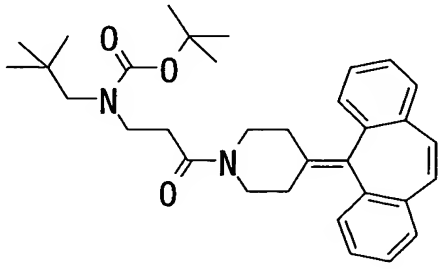
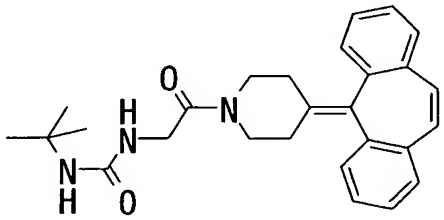
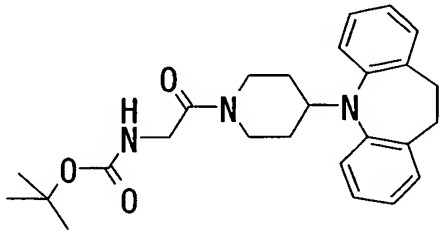
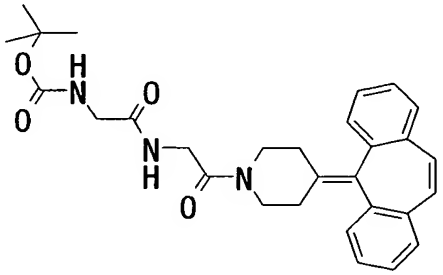
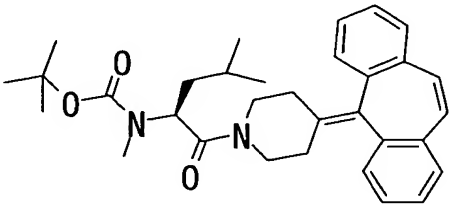
26		30	
27		31	
28		32	
29		33	

Table 5

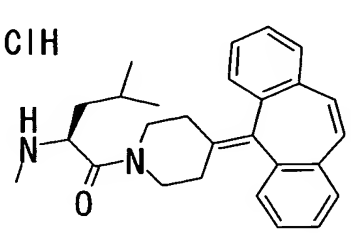
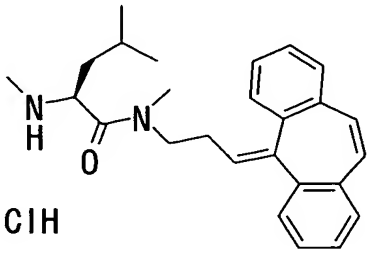
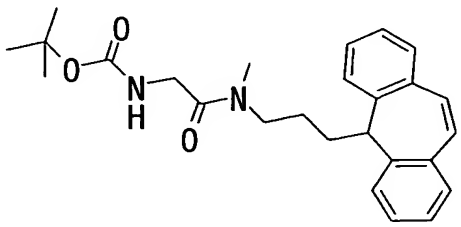
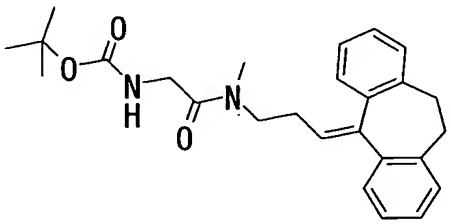
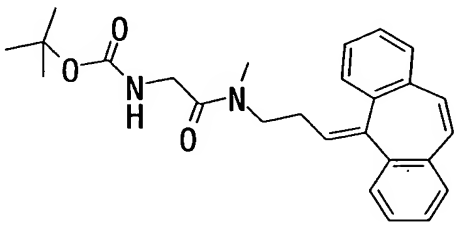
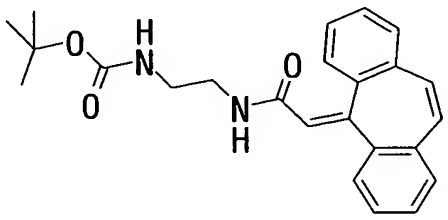
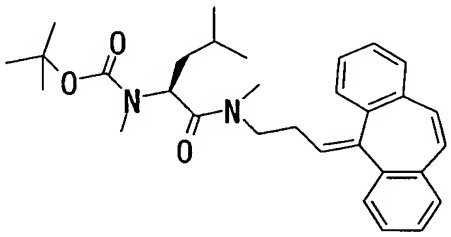
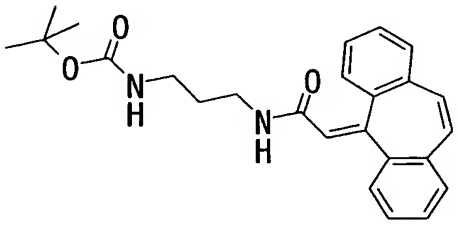
Ex.	Structural formula	Ex.	Structural formula
34		38	
35		39	
36		40	
37		41	

Table 6

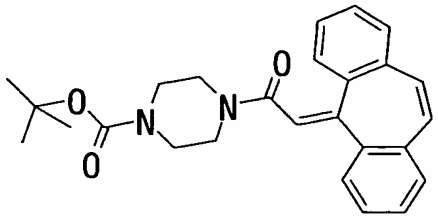
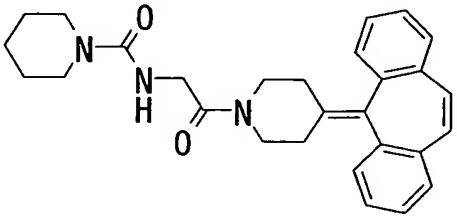
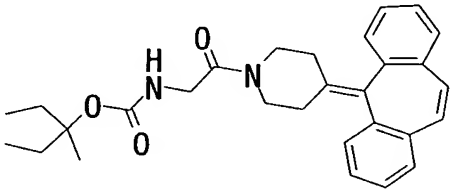
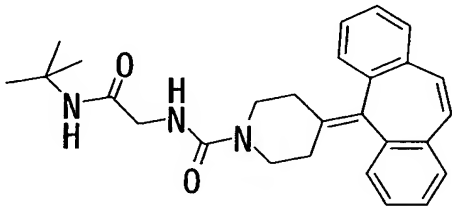
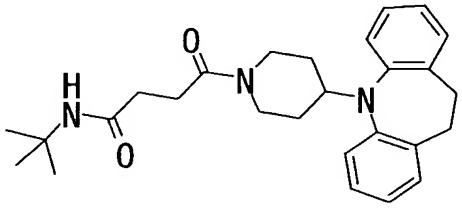
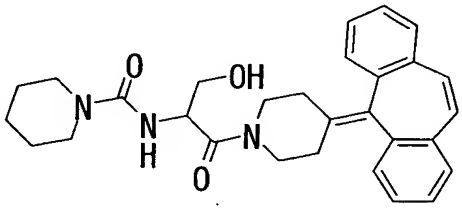
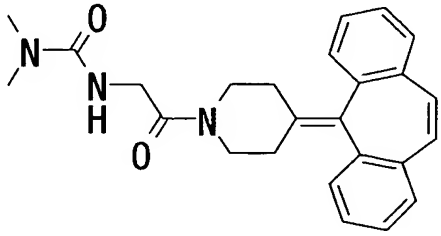
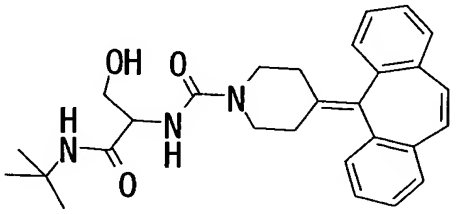
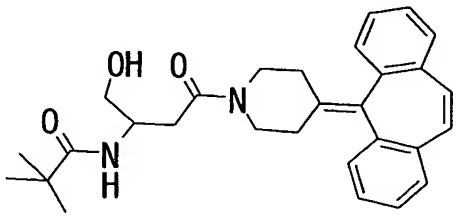
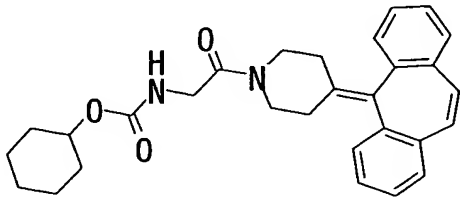
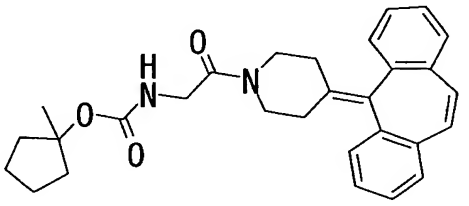
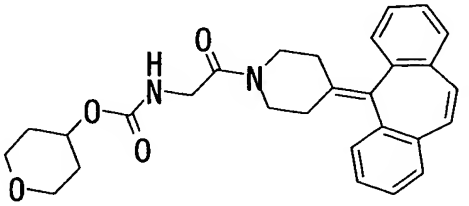
Ex.	Structural formula	Ex.	Structural formula
42		46	
43		47	
44		48	
45		49	

Table 7

Ex.	Structural formula	Ex.	Structural formula
50			
51			
52			
53			

(Test Example) Inhibitory activity on N-type calcium channel (fluorescence dye method):

Human neuroblastoma cells IMR-32 were obtained from ATCC (American Type Culture Collection). The medium used was a Phenol Red-free Eagle minimum essential medium containing earle's salts (GIBCO) supplemented with 2 mM of L-glutamine (GIBCO), 1 mM of sodium pyruvate (pH 6.5) (GIBCO), antibiotic / antimicotic mixture (GIBCO) and 10 % fetal calf serum (Cell Culture Technologies). Three ml of $1x10^5$ cells/ml IMR-32 cells were spread on the glass bottom of a dish (Iwaki Glsss Co., Ltd.) having a diameter of 35 mm which had been treated with poly-L-lysin (SIGMA) and collagen (COLLAGEN VITROGEN 100; Collagen Co.). After the culture for 1 day, 1 mM (final concentration) of dibutyl cAMP and 2.5 μM (final concentration) of 5-buromodeoxyuridine (SIGMA) were added. After the culture for additional 10 to 14 days, the cells were subjected to the activity determination.

The medium for IMR-32 cells thus prepared was replaced with 1 ml of Phenol Red-free Eale minimum essential medium (GIBCO) containing 2.5μM fura-2/AM (Dojin Kagaku, Co.) and earle's salts supplement, and the incubation was conducted at 37°C for 30 minutes. Then the medium was replaced with a recording medium (20 mM of HEPES-KOH, 115 mM of NaCl, 5.4 mM of KCl, 0.8 mM of MgCl2, 1.8 mM of CaCl2 and 13.8 mM of D-glucose). Antagonistic activity on N-type calcium channel was determined and analyzed using a fluorescence microscope (Nikon Corporation) and an image analysis device ARGUS 50 (Hamamatsu Photonics). In particular, a recording medium (20 mM of HEPES-KOH, 115 mM of NaCl, 5.4 mM of KCl, 0.8

mM of $MgCl_2$, 1.8 mM of $CaCl_2$ and 13.8 mM of D-glucose) containing 1 μM of Nifedipine was given to the cells by perfusion by a Y-tube method for 2 minutes. Then a stimulating agent containing 60 mM of potassium chloride was rapidly given by the Y-tube method. The calcium concentration change in the cells in this step was shown as the N-type calcium channel activity. Then stimulating agents containing 60 mM of potassium chloride and 0.1, 1 or 10 μM of the test compound were successively and rapidly given to the cells by the Y-tube method to determine the change in the intracellular calcium concentration. The inhibitory activity on N-type calcium channel was calculated from the inhibition rate (%) at a concentration of 10 μM.

(Test Example) Inhibitory activity on L-type calcium channel:

The inhibitory activity of the new diarylalkene derivatives and diarylalkyl derivatives of the present invention to inhibit L-type calcium channel was determined by the following method in which the relaxation response against the KCl-induced contraction of isolated rat thoracic aorta was employed.

1) Method of preparation of rat thoracic aorta:

The slips of thoracic aorta isolated from a Wistar rat were used. The aorta was cut to obtain ring-shaped samples having a width of about 3 mm. The endothelial cells of the samples were mechanically removed. The samples were suspended in a strain gage in Tyrode's solution (158.3 mM of NaCl, 4.0 mM of KCl, 1.05 mM of $MgCl_2$, 0.42 mM of NaH_2PO_4, 10 mM of $NaHCO_3$, 2 mM of $CaCl_2$ and 5 mM of glucose) in which a gaseous mixture of O_2 (95 %) and CO_2 (5 %) was introduced. A static tension of 2 g was applied thereto. The tension of the blood vessel was amplified with a transducer and a tension amplifier (EF-601G; Nihon Koden Corporation) and recorded with a multi-pen recorder (Rikadenki Kogyo

Co., Ltd.). The experiments were conducted at 37°C.

Table 8 shows the results of the measurement of the antagonistic activities on N-type calcium channels (inhibition rate at 10 μM: %) and L-type calcium channel (pIC50). The value of pIC_{50} indicates the antagonistic activity of the test compound, i. e. the negative logarithm of the concentration of the test compound necessitated for the 50 % inhibition.

2) Measurement of relaxation response against KCl-induced contraction:

After the tension had been stabilized, the nutrient solution in the sample tank was replaced with High K^+ Tyrode's solution (112.3 mM of NaCl, 50 mM of KCl, 1.05 mM of $MgCl_2$, 0.42 mM of NaH_2PO_4, 10 mM of $NaHCO_3$, 2 mM of $CaCl_2$ and 5 mM of glucose) to conduct the contraction reaction. Thirty minutes after, the solution in the sample tank was replaced with the normal Tyrode's solution. The solution in the sample tank was again replaced with the High K^+ Tyrode's solution and the contraction reaction was observed. After attaining the maximum contraction reaction, the test compound was cumulatively added at intervals of 90 minutes to attain concentrations of 10^{-9}, 10^{-8}, 10^{-7} and 10^{-6} M. The inhibitory rate of the test compound against the maximum contraction response was employed as the index of the inhibitory activity on L-type calcium channels.

Table 8

Example	Antagonistic activity on N-type calcium channels at 10 μM inhibition rate (%)	Antagonistic action on L-type calcium channels pIC_{50}
1	67	6.0
9	83	6.3
11	77	6.4
16	75	5.9
24	78	6.0
41	76	5.9

From the results described above, it was confirmed that the new diarylalkene derivatives and diarylalkyl derivatives have a high, selective inhibitory activity on N-type calcium channels and that they are useful as therapeutic agents for pains and also various diseases related to N-type calcium channels.

[Effects of the Invention]

The new diarylalkene derivatives and diarylalkyl derivatives of the present invention have the selective inhibitory activity on N-type calcium channels. Thus, the new diarylalkene derivatives and diarylalkyl derivatives of the present invention provide a method for treating various diseases, for example, for treating brain injury caused by ischemia at the acute stage after the onset of cerebral infarction, cerebral hemorrhage (including subarachnoidal hemorrhage) or the like; for treating progressive neurodegenerative diseases such as Alzheimer's disease, AIDS related dementia, Parkinson's disease, cerebrovascular dementia and ALS; for treating neuropathy caused by head injury; for treating pain caused by spinal injury, diabetes or thromboangitis obliterans, neuropathic pain, migraine, visceral pain, cancerous pain,

and for treating various diseases associated with psychogenic stress such as bronchial asthma, unstable angina and irritable colitis, emotional disorder and withdrawal symptoms after addiction to drugs such as ethanol addiction withdrawal symptoms.

5

[Name of document] Abstract

[Abstract]

[Problem]

To provide novel compounds having a selective antagonistic effect on N-type calcium channel.

[Means for Solution]

Diarylalkene derivatives represented by the following general formula, its analogue and pharmaceutically acceptable salts thereof have N-type calcium channel antagonistic effect, and they are usable as active ingredients of therapeutic agents for treating diseases selected from brain injury caused by ischemia at the acute stage after the onset of cerebral infarction or cerebral hemorrhage, Alzheimer's disease, AIDS related dementia, Parkinson's disease, progressive neurodegenerative diseases, neuropathy caused by head injury, pain caused by spinal injury or diabetes, neuropathic pain, migraine, visceral pain, cancerous pain, bronchial asthma, unstable angina, irritable colitis or withdrawal symptoms after addiction to drugs.